Resistance training to prevent and improve type 2 diabetes: RESIST DIABETES

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A thesis submitted for the degree of

Doctor of Philosophy at the

School of Medical Sciences

RMIT University

January 2012

As the doctoral thesis supervisor of Brett A Gordon (MAppSc BAppSc ESSAM AEP), I certify that I consider this thesis 'Resistance training to prevent and improve type 2 diabetes: RESIST DIABETES' to be suitable for examination.

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Declaration of the Author

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

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Acknowledgements

I need to begin by thanking and acknowledging the efforts and contributions of my first primary supervisor Dr Steve Fraser. Without your persuasion to undertake a PhD program I would not be in this position now. For this and all your guidance along the way I wish to express my sincere thanks. To my current primary supervisor Dr Amanda Benson, your support, encouragement and challenging my ideas and thoughts to make me see another pathway has been of tremendous value and has helped shape me to be the researcher I am today. I am also grateful for the dedication you have shown towards me and the priorities that you have placed on my work. To Professor Stephen Bird, my co-supervisor throughout this journey, it has been your critical analysis of everything that has led me to hopefully report an objective interpretation of the data, without any preconceived bias of what it should show, or what would best fit a particular perspective and viewpoint.

I would also like to express my sincere thanks to the different clinicians and researchers that I have collaborated with throughout this journey. The contribution from Dr Dodie Pouniotis was invaluable for the comparison between flow cytometry and ELISA. The endocrinology team at Austin Health has provided me with many opportunities to try to recruit participants for my projects and this was especially lead by Professor Richard MacIsaac who has recently taken up a position at St Vincent's hospital. I would also like to thank Dr Anne Reutens, Professor David Dunstan and Associate Professor Jonathan Shaw who so generously provided an opportunity to work with them in undertaking the eight week exercise study. Your efforts are all appreciated.

It would be remiss of me not to mention my specific thanks to Dr Reutens, Associate Professor Shaw and Professor Dunstan in their work in obtaining funding from Diabetes Australia Research Trust (DART) which allowed us to undertake the eight week exercise study. I also need to thank the Australian Technology Network's Centre for Metabolic Fitness, who provided funding for the grant submitted by Dr Benson, Professor Bird and myself for the continuous glucose monitoring study. I also need to gratefully acknowledge the efforts of all the participants that were involved in this series of studies. Without them, none of this would be possible and so I thank you all for your willingness and participation in contributing to a body of knowledge that has also allowed me to submit this PhD thesis.

And finally to my family. Your love, support and encouragement has been of great value to me right throughout these last few years. Listening to all my hardships involved in recruitment and data collection and analysis and then to remind me of the great opportunity that I have had has fuelled my motivation to undertake this work. I also thank you for your efforts in making my home life so much easier so that I could focus on my studies, this was very much appreciated. Especially the understanding and love from my wife Genevieve. The 4.30am starts where I was tip toeing around trying not to wake you, and then not getting home until 8pm or later, and you would always greet me with a smiling face. It was also your encouragement that saw me continue this journey through all the ebbs and flows of "is this all going to be worth it?" Well I can emphatically say now that yes it was all worth it and with your support and now the excitement of our two little babies, this is the results of all that hard work. From the bottom of my heart, thank you, I really appreciate all of your efforts and I look forward to the next chapter in our lives.

"Those who think they have not time for bodily exercise will sooner or later have to find time for illness." – Edward Stanley

Publications and Submissions

Parts of the work published in this thesis have been published or submitted for publication and are under review, or have been presented in the following forums:

Peer Reviewed Journal Articles (Appendix A)

- **Gordon BA**, Benson AC, Bird SR, Fraser SF. Resistance training improves metabolic health in type 2 diabetes: A systematic review. Diab Res Clin Pract 2009;83(2):157-175
- **Gordon BA**, Fraser SF, Bird SR, Benson AC. Reproducibility of multiple repeated oral glucose tolerance tests. Diab Res Clin Pract 2011; 94(3):e78-e82
- **Gordon BA**, Fraser SF, Bird SR, Benson AC. Insulin sensitivity in response to a single resistance exercise session in apparently healthy individuals. J Endocrinol Invest 2011; In press: DOI: 10.3275/7972

Manuscripts Submitted for Publication

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. Markers of insulin sensitivity and inflammation are not modulated by a single session of resistance exercise in inactive individuals
- **Gordon BA**, Bird SR, MacIsaac RJ, Benson AC. Resistance and aerobic exercise impair glucose tolerance in the 24 hours immediately following the exercise bout

Peer Reviewed Scientific Conference Presentations

Oral Presentations (Appendix B)

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. (2010). Leptin and adiponectin responses to a single session of resistance exercise. Oral presentation at Higher Degree by Research Student Conference - Presenting Tomorrow's Knowledge, RMIT University, Melbourne, Australia, 20 October 2010.

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. (2011). A single session of resistance exercise does not modulate insulin sensitivity or adipocytokine markers of inflammation in individuals with and without type 2 diabetes. Oral presentation at Higher Degree by Research Student Conference – Vision to Reality, RMIT University, Melbourne, Australia, 21 October 2011.

- **Gordon BA**, Bird SR, MacIsaac RJ, Benson AC. (2012). Continuous glucose response to resistance and aerobic exercise is similarly impaired in individuals with insulin requiring type 2 diabetes. Oral presentation at ESSA conference, Gold Coast, Australia, 19-21 April 2012

Poster Presentations (Appendix C)

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. (2009). A 4-day time course for insulin sensitivity in response to a single bout of resistance exercise in healthy 40-60 year olds. Poster presentation at 2009 ADS/ADEA Annual Scientific Meeting, Adelaide, Australia, 26-28 August 2009.

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. (2009). The insulin response following a single bout of resistance exercise varies between individuals with and without type 2 diabetes. Poster presentation at A Step Ahead: Higher Degrees by Research Student Conference 2009, RMIT University, Melbourne, Australia, 23 October 2009.

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. (2010) Consecutive oral glucose tolerance testing with or without prior resistance training does not affect insulin sensitivity in apparently healthy adults. Poster presentation at ESSA conference, Gold Coast, Australia, 9-11 April 2010

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. (2010) No change in insulin sensitivity following a single bout of resistance exercise in individuals with and without type 2 diabetes. Poster presentation at ESSA conference, Gold Coast, Australia, 9-11 April 2010

- **Gordon BA**, Fraser SF, Bird SR, Benson AC. (2010) Consecutive oral glucose tolerance testing with or without prior resistance training does not affect insulin sensitivity in apparently healthy adults. Poster presentation at Higher Degree by Research Student Conference - Presenting Tomorrow's Knowledge, RMIT University, Melbourne, Australia, 20 October 2010.

- **Gordon BA**, Bird SR, MacIsaac RJ, Benson AC. (2011). Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes. Poster presentation at 2011 ADS/ADEA Annual Scientific Meeting, Perth, Australia, 31 August – 2 September 2011.
- **Gordon BA**, Bird SR, MacIsaac RJ, Benson AC. (2011). Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes. Poster presentation at Higher Degree by Research Student Conference – Vision to Reality, RMIT University, Melbourne, Australia, 21 October 2011.

Funding

The resistance and aerobic exercise response in individuals with insulin treated type 2 diabetes study was completed thanks to funding from the Australian Technology Network's (ATN) centre for metabolic fitness (Chapter 7).

The insulin sensitivity response to an eight week exercise intervention study was completed thanks to funding from the Diabetes Australia Research Trust (DART), (Chapter 8).

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Commonly used abbreviations

ACSM = American College of Sports Medicine

ADA = American Diabetes Association

AHA = American Heart Association

AUC = area under the curve

BMI = body mass index

CBA = cytometric bead array

CGM = continuous glucose monitor

CI = confidence interval

CRP = C-reactive protein

DXA = dual x-ray absorptiometry

ELISA = enzyme-linked immunosorbent assay

ESSA = Exercise and Sports Science Australia

FBG = fasting blood glucose

GLUT4 = glucose transporter 4

HbA1c = glycated haemoglobin

HDL-C = high density lipoprotein cholesterol

HOMA = homeostasis model assessment

IGT = impaired glucose tolerance

IL-6 = interleukin-6

IPAQ = international physical activity questionnaire

ISI = insulin sensitivity index

$kcal \cdot wk^{-1}$ = kilocalories per week

LDL-C = low density lipoprotein cholesterol

MBBA = multiplex bead array assay

MET = metabolic equivalents

OGIS = oral glucose insulin sensitivity index

OGTT = oral glucose tolerance

RCT = randomised controlled trial

TC = total cholesterol

TG = triglycerides

TNF-α = tumour necrosis factor-alpha

T2D = Type 2 diabetes

VO_{2peak} = peak oxygen uptake

WHO = World Health Organisation

1RM = one repetition maximum

Thesis Summary

Background

Type 2 diabetes is a condition of chronic hyperglycaemia and insulin resistance. Currently it is estimated that 1-2 million Australians have type 2 diabetes with this predicted to increase by 47% over the next 20 years. Treatment of type 2 diabetes is complicated through diabetes related conditions of retinopathy, neuropathy and cardiovascular disease. Exercise has been recommended to be the first line of treatment, followed by oral hypoglycaemic medications and reverting to exogenous insulin injections if the prior treatment modalities fail to control blood glucose levels. With this in mind, expert authorities have made recommendations about the type and volume of exercise that people with type 2 diabetes should complete. These recommendations however are hampered by limitations within the available literature, particularly around resistance training for individuals with type 2 diabetes, where the initial exercise guidelines from the American College of Sports Medicine cited only two randomised control studies investigating the efficacy of exercise in this population. While the volume of evidence available has increased, from which the most recent guidelines are based, there is still a genuine lack of understanding of how each mode of exercise contributes to metabolic health improvements and what the most efficient and effective prescription is. Previously, these recommendations have primarily centred around aerobic type exercise, however it has been theorised that this particular form of training, requiring extended durations at moderate-high intensities is not well tolerated by individuals with type 2 diabetes and that resistance training may be a modality that, with its short work periods followed by frequent rest periods, is an attractive alternative that provides similar benefits to aerobic type exercise.

Purpose

This PhD thesis set out to explore the acute and chronic effects of resistance exercise, prescribed in accordance with guidelines produced by expert authorities. An initial observation is that resistance exercise guidelines vary between authorities and appear to have little supporting scientific evidence derived from populations with type 2 diabetes. The aims of the series of closely linked studies presented in this thesis were to determine the effects of resistance exercise on insulin sensitivity and glucose control, and to generate data that may inform a more precise resistance exercise prescription for this population.

Assessment of reliability and validity of methods

A preliminary study investigated blood analysis techniques of cytometric bead array and the commonly used ELISA methods for the analysis of markers of diabetes pathophysiology. Blood samples from 18 individuals were analysed pre- and post-resistance exercise using both methods, with cytometric bead array not detecting tumour necrosis factor-alpha or interleukin-6 in any sample. However, these cytokines were detected using ELISA. Leptin was detected in samples using both techniques, with values from cytometric bead array correlating strongly with those from ELISA ($r = 0.93$, $p < 0.001$) despite overestimating the value by 115% ($p < 0.001$). This suggests that the cytometric bead array provides different concentration values to ELISA and may not be sufficiently sensitive to measure some adipose derived cytokines involved in the pathophysiology of type 2 diabetes, and which are thought to respond to exercise. Based on these findings, ELISA was the technique chosen to evaluate insulin and adipose derived cytokines throughout this PhD thesis.

Another preliminary study investigated the reproducibility of the oral glucose tolerance test (OGTT) to provide a consistent estimate of insulin sensitivity across four consecutive days in 10 apparently healthy individuals. Individual coefficients of variation for the oral glucose insulin sensitivity index (OGIS) and the Stumvoll insulin sensitivity index were 7.8% and 14.4% with no statistically significant difference between days, however individuals with impaired glucose metabolism showed greater variability. Therefore, the OGTT was deemed to be a suitable technique for assessing insulin sensitivity in the subsequent intervention study involving apparently healthy individuals, but not so for studies involving individuals with type 2 diabetes. Given this finding, other methods of estimating insulin sensitivity (homeostasis assessment modelling [HOMA] and adipocytokine markers of inflammation) and glucose tolerance (continuous glucose monitoring) were employed when investigating the exercise response in people with type 2 diabetes.

Acute resistance exercise intervention in apparently healthy individuals

Given the equivocal evidence surrounding the impact of a single session of resistance exercise on insulin sensitivity, the specific aim of this study was to investigate whether a single session of resistance-exercise modulated insulin sensitivity and how long any changes were present. Oral glucose tolerance test derived mathematical equations (OGIS) shown to correlate with the euglycaemic-hyperinsulinaemic clamp were used to estimate insulin sensitivity. The OGTT was performed prior to exercise and on four consecutive days following exercise to track the insulin sensitivity response over 96 hours in 10 apparently healthy individuals. This study found a clinically meaningful impairment of insulin sensitivity (increase in OGIS $\geq$ 52.7 $ml \cdot min^{-1} \cdot m^{-2}$) over four days in people unaccustomed to resistance exercise. Thereby indicating that, a single session of

resistance exercise in apparently healthy individuals may impair insulin sensitivity for up to four days. If a similar response is not evident in people who regularly undertake resistance exercise, it leads to the possibility that frequent, regular sessions of resistance exercise are required to overcome the potentially adverse short-term effects of a single session of resistance exercise. Additionally, novice exercisers and their advisors should be aware of this when undertaking an exercise regimen.

Acute resistance exercise intervention in individuals with type 2 diabetes

The data investigating the acute effects of resistance exercise in people with type 2 diabetes have typically used OGTTs to estimate insulin sensitivity. Given the earlier finding from this thesis that OGTTs are probably inappropriate to use in this population, the specific aim of this study was to investigate whether individuals with type 2 diabetes responded in a similar way to a single session of resistance exercise as apparently healthy individuals. This study used indices of insulin sensitivity from fasting glucose and insulin concentrations (HOMA2) in 10 individuals with type 2 diabetes and 10 apparently healthy individuals, and found no group by time interactions ($p > 0.05$) for fasting glucose, fasting insulin, insulin resistance or insulin sensitivity. Although significant differences between individuals with and without type 2 diabetes for insulin sensitivity and insulin resistance were present at baseline ($p < 0.05$), these disappeared at 72 hours following the session. Additionally, adipocytokine markers of inflammation were not significantly altered 24 hours after the session ($p > 0.05$). This suggests that individuals with type 2 diabetes don't experience any improvement or impairment to insulin sensitivity between 24 hours and 72 hours following a single session of resistance exercise. It is possible however, that by using these 'snapshot' methods to investigate insulin sensitivity, any transient response, occurring within the first 24 hours was missed.

Therefore, methodologies that give a more complete picture by sampling more frequently or continuously would be very useful.

Resistance and aerobic exercise response in individuals with insulin treated type 2 diabetes

Continuous glucose monitoring has been used recently to indicate that individuals with type 2 diabetes can spend up to 40% of a 24-hour period in a state of hyperglycaemia (blood glucose $\geq$ 10 $mmol \cdot L^{-1}$). This randomised cross-over study compared the continuous blood glucose response to a single session of resistance exercise with a single session of aerobic exercise in eight males with type 2 diabetes requiring insulin treatment. Continuous glucose monitoring was performed for one day prior to exercise and for three days following a single session of exercise. This indicated an increased ($p = 0.006$) area under the 24-hour glucose curve in the initial 24 hours following both resistance and aerobic exercise that then returned to pre exercise levels in the 48-72 hour time period. However, there was no statistically significant change in the amount of time spent in hyperglycaemia following either exercise intervention ($p = 0.11$). So, whilst chronic exercise participation has been shown to improve glucose tolerance and control, an acute bout of unfamiliar exercise appears to adversely impair glycaemic control, and regular sessions of exercise may be required to overcome the apparent transient impairment to glycaemic control.

Insulin sensitivity response to an eight week exercise intervention

With the earlier findings from this thesis indicating a potential impairment of insulin sensitivity and glucose tolerance from a single session of resistance exercise, the aim of

this randomised controlled trial was to investigate whether a period of eight weeks of, thrice weekly, exercise training resulted in any initial or lasting improvements to insulin sensitivity. The indicators used were: indices from fasting glucose and insulin concentrations (HOMA2) and adipocytokine markers of inflammation. Thirty-eight individuals with type 2 diabetes treated with oral hypoglycaemic medications were randomised to complete either resistance exercise, aerobic exercise or flexibility exercise (control condition) and completed follow-up measures at two, four and seven days after the final exercise session. Repeated measures ANOVA revealed no group by time interaction, but did identify a significant time effect ($p = 0.04$) in response to eight weeks of exercise for fasting glucose, where the glucose level seven days after the final session was significantly higher than the glucose level two days after the final session. Interestingly, although not statistically significant, glucose was lower than baseline at 48 hours after the final session for those completing both aerobic and resistance exercise, before increasing in the aerobic group and being maintained in the resistance group. A significant group by time interaction was found for concentrations of adiponectin ($p = 0.04$) and a time effect for leptin where concentrations were reduced two days after the final session but increased significantly from there at seven days after the final session. Therefore, following the exercise prescription guidelines for eight weeks does not appear to provide any lasting improvement to insulin sensitivity. It appears possible though, that the exercise prescription guidelines are inadequate for improving metabolic health in individuals with type 2 diabetes, or that exercise needs to be performed on an ongoing basis with any changes being due to an acute response to the last exercise session, and that this may be lost within 48 hours (i.e. before the first post-intervention sampling time point in this study).

Overall conclusions

The results of these closely linked studies suggest that resistance exercise is safe to perform in individuals with type 2 diabetes as there were no significant adverse events or lasting impairments to any diabetes related outcomes. It appears however, that individuals with type 2 diabetes may respond differently to a single session of resistance exercise than apparently healthy individuals. It is also evident that unfamiliar resistance exercise leads to short-term impairments in insulin sensitivity and glucose tolerance in a similar way to a single session of aerobic exercise. While not being statistically significant, the difference in the trends of the glucose and insulin response to eight weeks of exercise between resistance and aerobic exercise, indicate that the mechanisms of regulating glucose tolerance are likely to be different, however this thesis does not shed any further light on the mechanisms involved. Given the overall conclusion from this series of studies is that no metabolic improvements are evident from either a single session or eight weeks of exercise training three times a week, future research should investigate the frequency, intensity and duration of resistance exercise that is required to induce metabolic benefits in individuals with type 2 diabetes.

Chapter 1

Introduction

1. Introduction

1.1. Type 2 Diabetes

Type 2 diabetes encompasses a group of metabolic conditions characterised by high concentrations of blood glucose, termed hyperglycaemia. Hyperglycaemia occurs as a direct result of defects in insulin secretion or insulin action alone, or a combination of both [1]. Symptoms of hyperglycaemia include passing large amounts of urine over a short period of time (polyuria), feelings of excessive thirst (polydipsia), marked weight loss, being excessively hungry (polyphagia) and also having blurred vision [2]. All of these symptoms may indicate the presence of diabetes mellitus and the need for further investigations. From a health perspective, it is important to note that a degree of hyperglycaemia sufficient to cause pathological and functional changes in target tissues may be present for an extended duration of time before being detected as diabetes mellitus [1] and hence, responding to and addressing early indications is imperative.

There are several classifications of diabetes mellitus and further classifications of impaired glucose regulation. Insulin dependent diabetes mellitus (IDDM), or more commonly known as type 1 diabetes or juvenile-onset diabetes is resultant from a cellular-mediated autoimmune destruction of the β-cells of the pancreas [3-5]. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that first occurs or is recognised during pregnancy [3-5]. Non-insulin dependent diabetes mellitus (NIDDM), or more commonly type 2 diabetes (T2D) encompasses individuals who are resistant to insulin and usually have some form of relative (rather than absolute) insulin deficiency and do not require exogenous insulin to survive but may require it as a treatment method [3-5]. Further to these classifications, individuals who have mild hyperglycaemia that does not meet criteria for the diagnosis of diabetes mellitus can be

classified as having either impaired glucose tolerance (IGT) or impaired fasting glucose depending on their fasting blood glucose concentration. These individuals are often referred to as having pre-diabetes and are at significantly increased risk of developing T2D [3-5].

Type 2 diabetes and IGT are defined by varying degrees of glucose intolerance and insulin resistance with diagnosis criteria traditionally based on plasma glucose and serum insulin response to an oral glucose challenge through an oral glucose tolerance test (OGTT) [3-5]. The specifics of glucose tolerance will be discussed in depth later, however essentially IGT is caused through either a lack of insulin secretion, or an inferior capacity to respond to insulin and transport glucose into the muscle for use as a fuel at the peripheries. It is recommended to complete an OGTT when fasting plasma glucose is in the borderline range, as it is the most sensitive test to detect a mild disturbance of glucose metabolism [6]. However, despite the sensitivity of the OGTT, there has been a recent shift towards using glycated haemoglobin (HbA1c) levels to diagnose diabetes [7].

Diabetes mellitus is associated with a number of long-term complications including retinopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, and amputations through gangrene [6]. People with diabetes are also at increased and accelerated risk of developing atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease [8]. Furthermore, hypertension and abnormal lipid metabolism are also regularly found in this population [9]. Consequently a reduced life expectancy, significant morbidity due to specific diabetes related micro-vascular complications and also the increased risk of macro-vascular complications listed above, along with a decreased quality of life have all been

associated with diabetes mellitus [10-12]. This has been substantiated in a recent Australian study which evaluated the chronic complexity of diabetes mellitus in terms of quality of life and found that as the degree of glucose tolerance worsened, the physical health and functional abilities of the affected person became steadily worse [13].

This also has great economic cost to the individual with T2D, the government and the overall population. Apart from the other health issues associated with T2D mentioned above, males and females have 3.1 and 0.6 more lost work days respectively per year while bed days are increased by 7.9 and 8.1 in males and females respectively with T2D compared to those without T2D [14]. The financial cost of incurring a lost workday was estimated in 2002 to be an average of $168 with the cost of a bed day estimated to be 40% of the cost of a lost work day [14]. Given these estimates, the cost of lost productivity to the individual with T2D was approximately $1500 in 2002 and given the increases in wages and cost of living over the last decade, this is likely to be more now. Further, in the USA alone in 2002, the direct costs of treating T2D (including hospital admissions, doctors fees, emergency services fess and medication costs) and the indirect costs through lost productivity were estimated to be 131,672 million dollars and this was predicted to increase to 156 billion dollars in 2010 and to 192 billion dollars in 2020 [14]. In Australia, the total direct and indirect costs of having diabetes has been estimated to be $5360 per person per annum [15], with this cost being 2.4 times higher in people suffering micro-vascular and macro-vascular complications compared to those without complications. Additionally, the government provides annual subsidies for people with diabetes through the forms of pensions and sickness benefits totalling an average of $5540 per person [15]. Given the increasing prevalence of T2D, the total cost of care for this condition is likely to increase at a similar rate. Therefore, an increased focus should

be given to primary prevention and low cost treatments for T2D which can be achieved through increasing levels of physical activity.

1.1.1. Epidemiology of Type 2 Diabetes

Metabolic conditions such as T2D and IGT are currently increasing in prevalence in Australia and abroad [16, 17]. Global estimates in 1995 reported approximately 135 million adults above the age of 20 years had diabetes [18]. It was also reported that the prevalence of diabetes would increase in developed countries (which includes Australia) by 27% to a total prevalence of 7.6% by the year 2025 [18]. While in themselves these are damning figures for population health, it may be somewhat underestimated. Looking closely at the figures reported for Australia in the same study, by the year 2025 it was estimated that the total population of Australia would be 18.374 million with a diabetes prevalence of 3.3% [18]. However, reports from the Australian government indicate the total population reached 20 million in mid 2007, well above what it was estimated to be by 2025. In the year 2000, the estimated number of adults with diabetes globally had increased from 135 million as previously reported to approximately 171 million, an increase of approximately 36 million and an 11% increase on the projected year 2000 number of 154 million adults [19]. The projected prevalence for 2025 and 2030 are again markedly different with the first projection indicating that almost 300 million adults would have diabetes worldwide compared to the more recent estimate of 366 million adults to have diabetes by 2030 [18, 19]. The most recent update estimated global prevalence of diabetes by completing statistical analyses on literature previously published and identified from countries within the United Nations [20]. These estimates suggest that in 2010 the global prevalence of diabetes was 6.4% consisting of some 285 million adults between the age of 20 and 79 years, and is predicted to increase to 7.7% of

the population consisting of some 439 million adults of the same age by the year 2030, which is considerably different to the previous estimates for the prevalence of diabetes in the year 2030 of 366 million adults [19]. Further estimations from the World Health Organisation from a systematic analysis of the literature suggest that the prevalence of diabetes in adult males was 9.8% and 9.2% in adult females [21].

The most recent population study carried out in Australia, reported almost 10 years ago, indicated that the total diabetes prevalence of known and newly diagnosed diabetes was 7.4% [17]. This however, rose to 9.4% when considering only those aged 40-74 years, with a greater number of males being affected than females. A recent study of older white Australian residents in New South Wales (NSW) concurred with these data, reporting a 9.3% incidence in diabetes at 10 years follow-up after entering the study without a diagnosis of diabetes [22]. This is much greater than the estimates of 2.7% for the year 2000 and 3.3% for the year 2025 reported by the earlier global estimates [18]. These figures from NSW in Australia are very similar to those of the United States of America (USA) where it was reported that the total prevalence for diagnosed and undiagnosed diabetes in 1999-2000 was 8.3% of their total population [23]. The Australian population data from 1999-2000 [17] was followed up 5 years later with a response rate of 60% and reported an incidence of type 2 diabetes of 4.3%, with again a higher prevalence in males compared to females [24]. The most recent National Health Survey conducted by the Australian Bureau of Statistics in 2007-08 indicated a prevalence of diagnosed diabetes of 4%, with 88% of these cases being T2D. This estimate is likely to understate the actual prevalence due to not taking into account un-diagnosed cases which have been estimated to be at least that of diagnosed cases [25].

When conditions of impaired fasting glucose and IGT are included with T2D, the total prevalence in the Australian population greater than 25 years of age having abnormal glucose tolerance was 23.7% with the prevalence reaching 53.1% for people aged 75 years or older [17]. This figure compares unfavourably to that of the USA where they report a total prevalence of abnormal glucose tolerance of only 14.4% and increasing to 33.6% by the time they reached 60 years of age [23]. This highlights potential differences between the American and Australian populations in terms of physical activity levels and dietary intake and the varied approaches taken in managing, diagnosing and reporting diabetes.

Therefore, T2D is a significant medical condition that affects large numbers of people throughout the world and can have dramatic effects on other organs and an individual's health status. Given this, it is important to understand the pathophysiology involved in glucose tolerance and T2D so that effective and efficient treatment regimens can be determined and prescribed.

1.2. Pathophysiology of Glucose Tolerance

Maintenance of normal glucose tolerance following a meal or ingestion of glucose is dependent on three events occurring in a tightly coordinated response. These events include stimulating the secretion of insulin from the pancreas, insulin-mediated suppression of endogenous glucose production via the resultant hyperinsulinaemia, and insulin-mediated stimulation of glucose uptake by peripheral tissues [26]. Hyperglycaemia is a well-established result of metabolic conditions such as T2D and IGT, caused through increased hepatic glucose production due to an insulin secretion abnormality and hepatic resistance to insulin [27]. This means that abnormal glucose

tolerance can be a result of either a defect in insulin secretion or insulin action or a combination of the two, where normal insulin action involves the suppression of hepatic glucose production and enhancing glucose uptake at the peripheries, especially at the muscle [26]. Factors known to contribute to abnormal glucose tolerance include obesity, physical inactivity and genetics.

Decreased insulin action can also be referred to as insulin resistance, where insulin resistance is classically defined as a state of decreased responsiveness of target tissues to normal circulating levels of insulin [28]. Skeletal and cardiac muscle, adipose tissue and the liver are the primary targets for insulin with skeletal muscle responsible for approximately 80% of all glucose uptake [28, 29]. In conditions of insulin resistance the ability of insulin to mediate glucose uptake is impaired and hepatic glucose production is no longer inhibited [30]. This results in greater concentrations of glucose in the blood since glucose is unable to be taken up and used by the target tissues at the same rate, thereby resulting in a state of hyperglycaemia.

In a normal state of glucose homeostasis, approximately 85% of endogenous glucose production is derived from the liver, while the remaining 15% is derived from the kidney with glycogenolysis and gluconeogenesis processes contributing equally to basal hepatic glucose production [29]. There is unequivocal evidence indicating hepatic resistance to insulin in conditions of T2D, which is substantiated by the impaired ability of insulin to suppress the hepatic glucose production [26]. This results in a constant flow of glucose entering the blood stream from the liver and producing the condition of hyperglycaemia in either the basal or fasting state [27]. Research indicates that insulin inhibits the hepatic

glucose production and release through blocking gluconeogenesis and glycogenolysis [28]; both of which increase in people with T2D.

Skeletal muscle is the most insulin sensitive tissue in the body, however in individuals with T2D, muscle tissue becomes resistant to insulin [26]. This is reportedly due to disruptions in glucose transport leading to defective muscle glycogen synthesis [28]. Glucose transport through adipocytes and myocytes is increased when insulin stimulates the translocation of the glucose transporter 4 (GLUT4) from an intracellular pool to the plasma membrane [28]. This occurs when insulin binds to its receptor on the plasma membrane and activates the tyrosine kinase activity and autophosphorylation of specific tyrosine residues of the receptor, initiating the intracellular signalling cascade [30]. This insulin signalling cascade in relation to glucose transport is not fully understood, however two main pathways have been identified. These are the phosphatidylinositol 3-kinase (PI-3K) and mitogen-activated protein (MAP) kinase pathways.

The PI-3K pathway is initiated by tyrosine phosphorylation of one of the insulin receptor substrate family (IRS-1/2/3/4) which associates with the p85 regulatory subunit of the PI-3K and activates the enzyme phosphatidylinositol 3,4,5-phospate (PIP3). This results in the activation of protein kinase B (otherwise known as Akt) and other downstream effector molecules, mediating the metabolic response to insulin, which includes the translocation of GLUT4 [30]. The MAP kinase pathway is the other main pathway which begins with phosphorylation of the Shc adaptor protein or insulin receptor substrate, which binds Grb2 and activates Ras which in turn binds and disinhibits Raf, activating another kinase (MEK1), which activates extracellular signal-regulated kinases ERK1 and

ERK2. These mediate the mitogenic and proinflammatory responses of insulin signalling [30].

Defects in insulin receptor function, insulin receptor-signal transduction pathway, glucose transport and phosphorylation, glycogen synthesis and glucose oxidation all contribute to a state of insulin resistance [26]. It is then reported that due to the defect in the insulin receptors, the PI-3K pathway is impaired from the reduced ability of the insulin receptor and IRS-1 to activate tyrosine phosphorylation and a decreased association of p85 protein [31]. This decreases the number and availability of the GLUT4 to transport glucose from the blood stream into the muscle. The MAP kinase pathway however, remains intact and continues to mediate the mitogenic and proinflammatory responses which contribute to atherosclerosis and other associated health conditions including hypertension, dyslipidaemia, insulin resistance and T2D [31].

Impaired insulin secretion is a major contributor to the pathophysiology of glucose intolerance, with all individuals with T2D and elevated fasting plasma glucose concentrations having a defect in insulin secretion [26]. Initially the pancreas has the capacity to up-regulate the production of insulin enabling the body to mediate the disposal of glucose through the peripheries and inhibit hepatic glucose production so that a degree of normoglycaemia is maintained through being in a state of hyperinsulinaemia [27]. However, prolonged hyperfunction of the pancreas (hyperinsulinaemia) can lead to β-cell exhaustion, beginning the cascade of hyperglycaemia with a gradual progression towards T2D [30]. This is a result of abnormal β-cell function via a progressive loss of pancreatic islet β-cells resulting in insulin deficiency and a requirement to replace insulin exogenously [27]. Of which, the major pathological consequence is non-insulin

dependent diabetes mellitus and the series of complications associated with this like chronic kidney disease, peripheral neuropathy and retinopathy can develop.

Theories of glucotoxicity and lipotoxicity have also been suggested in T2D, where prolonged high concentrations of glucose impair insulin gene transcription and lead to decreased insulin synthesis and secretion [29]. The lipotoxicity theory suggests increased free fatty acids within the β-cells results in the conversion of long-chain fatty acids to their fatty acyl-CoA derivatives, which over time causes increased nitric oxide and increased expression of inflammatory cytokines which actually impairs β-cell function and insulin secretion [29]. This indicates that a number of factors including age, genetics and insulin resistance are implicated in the failure of the β-cell to perform its natural function adequately and maintain the body in a state of normoinsulinaemia with resultant normoglycaemia. While the pancreas has an excellent ability to be able to adapt to abnormal conditions, a modest reduction in β-cell mass of 20%-40% can have major implications on glucose homeostasis [29].

While the pathophysiology of T2D is a complicated sequence of events, in essence, it can be expressed as the body's inability to regulate glucose production efficiently with high circulating levels of glucose increasing the risk for other associated conditions of retinopathy, neuropathy and renal disease. A number of different medications can be prescribed to reduce blood glucose levels through either stimulating further insulin production or improving insulin sensitivity with the final step being exogenous insulin prescribed to supplement naturally produced insulin [4]. Exercise is also a well-known beneficial treatment for T2D as it has the ability to impact the PI-3K pathway through increasing the availability of GLUT4 but also impacting the MAP kinase pathway

through increasing the quality of the muscle and improving its ability to take up greater amounts of glucose [32], and modulate concentrations of adipose derived cytokines which indicate sub-clinical levels of inflammatory disease [33]. Additionally, exercise has the ability to reduce the risk of some other predicting and contributing factors for T2D such as overweight and obesity [34].

1.3. Predicting and Contributing Factors

Research over the past decade has indicated that inflammation is a key feature of obesity and T2D [35], with reports identifying obesity as the most critical factor in the emergence of metabolic disease [36]. The population study of Australia carried out in 1999-2000 indicated that the overwhelming majority of people with diabetes were overweight (> 25 $kg \cdot m^{-2}$), or more likely, obese (> 30 $kg \cdot m^{-2}$) according to their body mass index (BMI) [17]. In a smaller sub-population study of older Australians, 16% of those who were obese at baseline progressed to a diagnosis of diabetes within 10 years [22]. Data from the National Health and Nutrition Examination Survey, 1999 to 2004 shows the increasing prevalence of diabetes with increased class of obesity up to an odds ratio of 5.1 for those who were class three obese [37], while in Australia, the odds ratio for abdominal obesity associated with diabetes is between two and five with a population attributable fraction of 47.4% for women and 38.0% for men [38]. However, obesity on its own or with a single additional trait of the metabolic syndrome is not a strong predictor of progression to diabetes, with only 6% of these people diagnosed with T2D [22]. When obesity was in addition to two or more traits of the metabolic syndrome the incidence of progressing to diabetes within 10 years increased to between 20-40% [22].

A large population sample of Australians aged 25 years or older reported a prevalence of overweight of 39% and obesity of almost 21% [39]. When BMI was replaced with a measure of waist circumference, overweight levels (94-102cm for men & 80-88cm for women) were reduced to a prevalence of 25%, with obesity prevalence (> 102cm for men & > 88cm for women) increasing to 30% [39]. Thus indicating large levels of truncal or abdominal obesity, which has been reported to be more metabolically active, and increasing the risk of T2D, coronary artery disease, cancer and premature death. Data from the Diabetes Prevention Program indicated that waist circumference was a better predictor of diabetes than BMI [40], probably due to its sensitivity of measuring central adiposity, although BMI was still able to significantly predict diabetes. Throughout the Asia-Pacific region it is reported that Australia has the greatest levels of overweight and obesity of any country at a staggering 60% of the population compared to a mere 5% of the Indian population being classified the same way [41]. This figure compares very closely to those reported for the USA, where in 2003-2004 66% of their population was either overweight or obese [42]. Childhood and adolescent levels of overweight have most recently been reported to be affecting 17% of the American population which has risen steadily from 14% only eight years ago [42]. In Australia, the most recent estimates of childhood and adolescent overweight and obesity were conducted in the 2007-08 National Health Survey [25], which reported that approximately 17% of children and adolescents aged 5-17 years were overweight and 8% were obese, this was up from a total of 20% meeting the criteria for overweight in 1995 [16].

Sedentary behaviour is also emerging as a significant contributor to T2D, with landmark findings of increased fasting plasma glucose and two-hour plasma glucose both being shown to increase significantly with every additional hour of television viewing time in

men and women [43]. Even in people without diagnosed T2D, increased amounts of sitting time have been associated with increased levels of overweight, increased triglycerides, increased two-hour plasma glucose and increased fasting insulin concentrations, while it has also been associated with reduced high-density lipoprotein cholesterol in women only [44]. Further, the detrimental effects of sitting time on components of the metabolic syndrome has also been shown to be independent of moderate-vigorous physical activity and all other lifestyle risk factors [45].

1.4. Exercise Recommendations

Exercise is widely accepted and recommended as part of the treatment plan for individuals with T2D and those with IGT to reduce the risk of progression to T2D. Aerobic exercise with an emphasis on endurance training is the main feature of most exercise guidelines released by the major exercise and medical associations. The latest position statement released by the American Diabetes Association (ADA) concludes that physical activity is a vital component of the primary prevention as well as management of T2D and must be viewed as a high priority [46]. Without making any specific recommendations of its own, it supports the position of the American Surgeon General's Report on Physical Activity and Health of completing 30 minutes of moderate intensity physical activity on most days of the week. The ADA report also indicates that high intensity resistance training may be suitable for young individuals with diabetes, but not for older individuals or those with long standing diabetes, and that moderate intensity resistance training with light weights and high repetitions can maintain or enhance upper body strength. This position statement reports why exercise is so beneficial for people with both type 1 and type 2 diabetes, but fails to enlighten on what type, volume and

intensity are required to achieve the benefits [46]. A summary of all the exercise guidelines for individuals with T2D can be found in Table 1.1.

1.4.1. Primary prevention of type 2 diabetes

The American College of Sports Medicine (ACSM) along with the American Heart Association (AHA) have recently updated their physical activity and public health recommendations [47] that were originally published with the Centers for Disease Control and Prevention (CDC) in 1995 [48]. This recommendation states that all healthy adults need to complete moderate intensity aerobic activity for a minimum of 30 minutes on five days each week or vigorous intensity aerobic activity for a minimum of 20 minutes on three days each week or a combination of the two [47]. It also states that adults will benefit from performing resistance training exercises on a minimum of two days each week, completing 8-10 different exercises using a weight that allows 8-12 repetitions of each exercise resulting in volitional fatigue.

Further to these recommendations the ACSM and AHA also released updated guidelines for older adults or adults older than 50 years with a chronic condition or functional limitation [49]. The aerobic activity guidelines for older adults are the same as the physical activity and public health guidelines with the intensity differing slightly from using MET values for moderate and vigorous intensities to using values on a 10 point scale and changes to heart and breathing rates. Similarly for the resistance training guidelines, the only notable difference is how many repetitions of each exercise should be achieved, being 10-15 where the effort is moderate to high. Here the ACSM recommends moderate intensity resistance training but acknowledges high intensity training is an option when older adults are supervised or when they have sufficient fitness

and experience to complete it. It is also recommended that older adults partake in flexibility and balance exercises on at least two days each week.

Table 1.1: Summary of exercise guidelines for those with type 2 diabetes.

Year	Recommending Body	Aerobic Exercise Guidelines	Resistance Exercise Guidelines	Notes	Exercise intervention RCT studies in T2D cited
2011	ESSA [50]	Minimum of 150 min per week at a moderate intensity (40-59% VO_2R or HRR) OR a minimum 75 min per week of vigorous intensity (60-84% VO_2R or HRR) exercise with no more than two consecutive days without exercising.	Minimum of 60 min per week of moderate to vigorous multi-joint exercises using large muscle groups. 8-10 exercises, 2-4 sets, 8-10 repetitions at 70-84% 1RM with 1-2 minute rest intervals. Complete 2 or more times a week.	Aerobic and resistance exercises should be completed attaining a minimum of 210 min per week at a moderate intensity or 125 min per week at a vigorous intensity.	8
2010	ACSM / ADA [51]	At least 150 min per week of moderate intensity (40-60% VO_{2max}) on at least 3 days per week with no more than 2 days between sessions.	5-10 exercises for upper and lower extremities, completing 1 set (but as many as 3-4) of 10-15 reps (progressing to 8-10) on 2 but ideally 3 days each week at a moderate (50% 1RM) or vigorous (75-80% 1RM) intensity.	Complete resistance training along-side aerobic training.	18
2009	AHA [52]	A minimum of 10 min on a minimum of 3 days a week accumulating 150 min of moderate intensity or 90 min of vigorous intensity a week.	3 days per week using all muscle groups progressing to 3 sets of 8-10 reps at 75-85% 1RM with 1-2 min rest between sets.	Patients with T2D should perform both aerobic and resistance exercise and minimise sedentary behaviours.	15
2004	ADA (technical review) [53]	At least 150 min per week of moderate intensity PA and/or 90 min of vigorous aerobic exercise on at least 3 days a week with no more the 2 days between sessions.	In the absence of contraindications, 3 times a week, progressing to 3 sets of 8-10 reps using a weight that cannot be lifted more than that amount. Including all major muscle groups.	Flexibility training is not recommended OR advised against.	5

Table 1.1 (Continued)

2004	ADA [46]	At least 3-4 sessions of aerobic exercise per week of 30-60 min duration at 50-80% VO_{2max}	High intensity resistance training for younger individuals but not older or those with long standing diabetes.		0
2003	CDA [54]	At least 150 min per week of moderate intensity PA on at least 3 days a week with no more the 2 days between sessions.	3 times a week, progressing from 1 set of 10-15 reps to 3 sets of 8 reps.		2
2000	ACSM [55]	3-5 PA sessions per week of 10-15 min duration but ideally 30 min at a low to moderate intensity (40-70% VO_{2max})	8-10 resistance training exercises for major muscle groups completed at least twice week. Complete a minimum of 1 set containing 10-15 reps.	Accumulate a minimum energy expenditure of 1000 $kcal \cdot wk^{-1}$ from aerobic activities with the addition of a well rounded resistance training program.	2

ESSA = Exercise and Sports Science Australia; ACSM = American College of Sports Medicine; CDA = Canadian Diabetes Association; ADA = American Diabetes Association; AHA = American Heart Association; reps = repetitions; VO_{2max} = maximal aerobic capacity; 1RM = one repetition maximum; min = minutes; PA = physical activity; VO_2R = VO_2 reserve; HRR = heart rate reserve

1.4.2. Treatment of type 2 diabetes

In a separate statement, the ACSM specifically endorse exercise as a treatment for T2D with recommendations to expend a minimum cumulative total of 1000 kcal·wk^{-1} from aerobic activities and in addition, complete a well-rounded resistance training program [55]. The resistance training program suggested, appears to be based on the previous public health recommendations from 1998 [56] and is very similar to the ACSM and AHA's updated recommendations of completing 8-10 resistance training exercises at least two days a week with a minimum of one set of 10-15 repetitions. While this at least gives practitioners something to work from it is still very much a generalised guideline based on limited scientific data from populations with T2D.

The Canadian Diabetes Association has also released physical activity recommendations for those with T2D, indicating that they should accumulate at least 150 minutes of moderate intensity aerobic exercise each week spread over at least three non-consecutive days [54]. They also suggest that if willing, individuals with T2D should be encouraged to accumulate greater than four hours of exercise per week and that all individuals with T2D should be encouraged to perform resistance exercise three times per week, progressing from one set of 10-15 repetitions to three sets of eight repetitions.

A technical review released by the ADA [53] only nine months following its position statement [46] gives much more detail regarding the issues surrounding type, volume and intensity for those with T2D. It recommends undertaking aerobic exercise to improve glycaemic control, assist with weight maintenance and reduce the risk of cardiovascular disease for at least 150 minutes per week at a moderate intensity and/or undertake at least 90 minutes per week of vigorous exercise. This should be distributed over a minimum of

three days a week with no more than two consecutive days without physical activity as insulin sensitivity is increased following a single bout of aerobic exercise for between 24 and 72 hours. It is noted however, that for long-term maintenance of significant weight loss, larger volumes of exercise may be helpful. Since the ACSM's (2000) resistance training guidelines for T2D were published, several resistance training studies have been published which have formed the basis of the guidelines by the ADA [53]. The ADA recommends resistance training be completed in the absence of contraindications, three times a week, progressing to three sets of 8-10 repetitions using a weight that cannot be lifted more than that quantity of repetitions [53]. Again this recommendation is based on the prescription in only a few randomised controlled trials (Table 1.1) and therefore has not been subjected to the same quantity of scientific investigation that the aerobic training guidelines have. Further research regarding the acute and chronic effects of resistance training specifically conducted on individuals with T2D in relation to training intensities and frequency is required to strengthen the basis of the guidelines, rather than taking a best guess developed from literature on other populations.

Taking a slightly different approach, the AHA released a scientific statement looking at the impact on cardiovascular disease of exercise training for people with T2D [57]. They reported many beneficial effects of exercise and recommend that exercise training be completed on at least three non-consecutive days a week with each session to last a minimum of 10 minutes and in addition, to minimise the amount of sedentary behaviours. Their guidelines for aerobic exercise are moderate intensity on 3-7 days per week accumulating 150 minutes per week or completing vigorous exercise on three days per week for an accumulated total of 90 minutes. They also recommend the completion of resistance training for the major muscle groups at a moderate to high intensity

progressing to three sets of 8-10 repetitions. While they recommend exercise on non-consecutive days, it is suggested that training five or more days a week may maximise the acute glucose lowering effect and the cardiovascular benefits. The authors [57] also state that caution should be applied to prescribing walking as it could easily be performed at lower intensities and therefore recommend that vigorous intensities should be targeted if tolerated with consideration of any contraindications, thereby suggesting the need to work at as high intensity as possible. This is a major point of difference from other guidelines.

In late 2010, the ACSM and the ADA released a joint position statement for exercise and T2D [58]. These guidelines recommend completing aerobic exercise at a moderate intensity (40-60% of maximal exercise capacity) on at least three days per week with no more than two consecutive days between sessions to achieve a volume of at least 150 minutes per week. They also recommend completing resistance training alongside aerobic training on at least two, but ideally three, non-consecutive days a week. This resistance training session should encompass 5-10 exercises for upper and lower extremities of the body, consisting of one set, but as many as 3-4 sets, of 10-15 repetitions (progressing to 8-10) at a moderate (50% of one repetition maximum) or vigorous (75-80% of one repetition maximum) intensity. Although there are a few more randomised controlled studies of exercise cited in these guidelines, it appears that not all randomised controlled trials have been considered.

Locally in Australia, the National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes [59] suggests that lifestyle modification (diet and physical activity) is an integral component of diabetes care. The Royal Australian College of General

Practitioners along with Diabetes Australia release a diabetes management document on an annual basis. The latest recommendations [60] for exercise and physical activity from this document reflect other diabetes association's views and the physical activity guidelines for Australian adults. It therefore recommends that individuals with diabetes, like all adults, should complete a minimum of 30 minutes of aerobic exercise which makes them 'huff and puff' on three or four days each week, or complete greater than 150 minutes of exercise each week [60]. It also outlines the risks involved with isometric exercise or heavy weight lifting, such as increases in blood pressure and sudden cardiac events, but identifies that resistance training programs using moderate weights and high repetitions can be part of an exercise program for those with T2D. These guidelines with respect of resistance training do not reflect the scientific research findings and are very conservative in this area, probably due to the document being aimed specifically towards general practitioners who typically have limited training and knowledge in regards to exercise prescription.

Very recently, Exercise and Sports Science Australia (ESSA) released a position statement relating to exercise prescription for patients with T2D [50]. Within this statement, ESSA recommend completing a minimum of 150 minutes of aerobic exercise per week along with two 30 minute sessions of whole-body resistance training, with no more the two consecutive days between exercise sessions. The authors also suggest that patient capabilities and interests be taken into consideration and state that any combination and volume is better than not completing exercise at all and will provide similar health benefits to those experienced if adhering to the guidelines, they will just take longer to be experienced [50].

The main type of exercise traditionally prescribed and recommended for people with T2D continues to be aerobic type exercise. However, as can be seen from the latest guidelines released since 2009, resistance type exercise is starting to be recommended more. It is concerning however, that between the major exercise and health organisations around the world, that there is no clear agreement on the type, duration, intensity or frequency that should be completed, especially with consideration to the resistance training guidelines. It is therefore evident that greater research is required to identify the optimal duration, intensity and frequency required of each type of exercise for the improvement and maintenance of blood glucose levels in individuals with T2D.

While resistance training is being increasingly advocated with new research reporting beneficial effects from this form of exercise, there are many issues that remain unresolved, especially in relation to individuals with T2D. Therefore, the following chapters of this dissertation will review the literature specifically in relation to resistance training and T2D followed by a series of closely linked acute and chronic investigations which will detail the acute metabolic responses to resistance exercise along with the chronic adaptations and health benefits gained from an ongoing resistance training program. As it is understood that resistance and aerobic exercise provide similar diabetes related benefits through common and different mechanisms, changes and responses from resistance exercise interventions will also be compared to those from aerobic type exercise to outline the potential differences between exercise types.

1.5. Aims

The primary aim of the research presented in this thesis was to establish the glucose, insulin and insulin sensitising effect from a single bout of resistance exercise and how

long those changes persisted. The secondary aim was then to determine if the period of time the changes were present for altered after a prolonged period of regular resistance exercise. The conflicting evidence base surrounding an acute bout of resistance exercise in which some [61-64] report improvements to insulin sensitivity at different time points in people with and without T2D compared to others who report no changes [62, 63, 65-68] points to the lack of evidence for the frequency of exercise required to alter blood glucose concentrations. It is also important to note that the longest follow-up time following a single session of resistance exercise is 36 hours and these have only been looked at in terms of pre and post exercise values. Additionally, it appears that the insulin and glucose responses following either a single session or long–term resistance exercise interventions have not been tracked over a number of days. The lack of agreement of the time frame for acute effects to remain has seen the follow-up period for chronic intervention studies be anywhere between two and four days following the final exercise session. However, the response to resistance exercise has not been sufficiently investigated to see exactly how long any changes might be present for following an ongoing period of resistance training.

Understanding the time course of the glucose and insulin responses is important to know as it has the ability to influence exercise training guidelines in terms of the required exercise frequency. The current guidelines for exercise frequency appear to be based on data obtained in healthy and athletic populations and then applied to clinical populations and therefore may not actually be the most appropriate for those with or at risk of developing T2D. It is also important to define the minimum efficacious exercise dose as currently large numbers of people with T2D do not meet the recommended exercise

volumes [69], so if it were possible to achieve and maintain metabolic improvements with less frequent exercise sessions, this would be a very important public health finding.

The following hypotheses were investigated over the course of this thesis:

i. That cytometric bead assay would be sensitive enough to accurately measure adipocytokines.
ii. That oral glucose tolerance tests repeated on four consecutive days would produce similar estimates of insulin sensitivity.
iii. That a single session of resistance exercise would not modulate insulin sensitivity in apparently healthy individuals.
iv. That a single session of resistance exercise would improve insulin sensitivity in people with type 2 diabetes when compared with apparently healthy individuals.
v. That a single session of resistance exercise would improve glucose control to a similar extent as that experienced following a single session of aerobic exercise.
vi. That compared to a sham exercise (flexibility training) control group; there would be no difference in the change to insulin sensitivity after aerobic or resistance exercise training.

Chapter 2

Resistance training improves metabolic health in type 2 diabetes: A systematic review

2. Resistance training improves metabolic health in type 2 diabetes: A systematic review

2.1. Preface

To accurately assess the gaps in the literature and guide future research a systematic review was undertaken. This chapter is based on a peer-reviewed paper published in Diabetes Research and Clinical Practice [70] (Appendix A). This paper has been cited numerous times, including in the most recent update of the exercise recommendations for individuals with type 2 diabetes published jointly by the American College of Sports Medicine [51] and the American Diabetes Association [71].

2.2. Introduction

The world-wide prevalence of type 2 diabetes (T2D) continues to increase [19] however, despite exercise being promoted as a vital part of the treatment process, exercise guidelines do not vary between prevention and treatment. For individuals with existing diabetes, specific benefits of exercise include increased insulin sensitivity, improved glycaemic control [72, 73], improved lipid profile and lower blood pressure [73]. Importantly, individuals with diabetes completing exercise training using various exercise modes for between eight weeks and 12 months have experienced decreased glycated haemoglobin (HbA1c) by clinically significant levels (0.6%), improved insulin sensitivity and reduced serum triglycerides [74].

The American College of Sports Medicine (ACSM) endorses exercise as a treatment method for people with T2D and recommends expending a minimum cumulative total of 1000 $kcal \cdot wk^{-1}$ of energy from aerobic activities [55]. The American Diabetes Association (ADA) has similar recommendations for at least 150 minutes per week of

moderate intensity aerobic physical activity and/or 90 minutes per week of vigorous aerobic exercise [53]. Accordingly, aerobic exercise has been the major focus for exercise-training studies due to consistent findings of improved glucose control [46, 75], however long-term compliance to these recommendations remains low [76] necessitating the investigation of an effective strategy to improve adherence rates.

Recently, resistance training has been the focus of increased research and it is suggested to improve glycaemic control and insulin sensitivity partially via similar mechanistic pathways to aerobic training [77], and partially through discrete pathways providing additive insulin signalling benefits. The focus on resistance training is in part due to a recognition that individuals with T2D, who are also likely to be obese or suffering from other co-morbidities, are likely to struggle to achieve the volume and intensity of aerobic training that's required to be effective [77, 78], and therefore compliance to resistance training may be higher. Both the ACSM and the ADA had included resistance training in their exercise prescription guidelines for younger individuals with T2D and for older individuals with T2D who were free from contraindications. The recommendations were; one set of 10-15 repetitions for 8-10 exercises twice a week [55] and, progressing to three sets of 8-10 repetitions three times a week [53]. These recommendations appeared to be largely based on information regarding healthy individuals and the few [79-82] randomised controlled trials of resistance training in individuals with T2D completed at the time that they were published. The authors of the ADA position statement do acknowledge the fact that prospective cohort studies have had a large influence over the content of the guidelines [53]. Recently the ACSM and the ADA released a joint position statement recommending that individuals with T2D complete both aerobic and resistance exercise [51] and this has been endorsed by Exercise and Sports Science Australia

(ESSA) who have also recommended the completion of both types of exercise [50]. However, it should be noted that significant improvements to insulin sensitivity in healthy individuals have been reported only when resistance training was performed three or more days a week [83] and the responses of individuals with diabetes may differ. Therefore the purpose of this chapter was to systematically review the literature on the effects of resistance training on the diabetes markers of glycaemic control and insulin sensitivity in individuals with T2D.

2.3. Methods

2.3.1. Search Strategy

Ovid MEDLINE (1950 to December 2011), and CINAHL (1982 to December 2011) electronic databases were searched on September 09 2011. First, three keyword and categorical searches were performed (i) 'diabetes', or 'diabetes mellitus', or 'type 2 diabetes mellitus'; (ii) 'weight lifting', or 'resistance training', or 'strength training', or 'weight training', or 'progressive resistance training', or 'circuit training'; (iii) 'glucose intolerance', or 'blood glucose', or 'glucose', or 'glucose metabolism disorders', or 'glucose tolerance test', or 'insulin', or 'insulin resistance', or 'diabetes complications', or 'haemoglobin A', or 'glycosylated haemoglobin A', or 'HbA1c'. Second, categories i to iii were combined using 'and', limited to humans and reported in the English language with duplicates removed. In addition, reference lists of all publications meeting the inclusion criteria were manually searched to identify any relevant studies not found through electronic searching.

2.3.2. Inclusion and Exclusion Criteria

Studies that met the following criteria were included in this review: (i) published in English (ii) cohorts were adults above the age of 18 years with T2D, (iii) a form of resistance training was included as an isolated intervention arm, (iv) it was an intervention study, (v) one diabetes marker (HbA1c, fasting glucose or insulin, insulin sensitivity) or an insulin signalling outcome were reported. Cross-sectional and observational studies, review or opinion/editorial papers were excluded along with studies that did not report diabetes or insulin signalling markers or studies that investigated only individuals without diabetes. Interventions that combined resistance training with another intervention (aerobic training or diet) or did not involve ongoing training were also excluded.

2.3.3. Statistical Analyses

To avoid misrepresentation of the presented data, a meta-analysis was not conducted due to the methodological differences in terms of frequency and intensity of training, along with the number and type of exercises completed. Clinical significance has been interpreted as a 0.6% improvement in HbA1c [74]. Effect sizes were not calculated as only eight papers included in the review provided enough information to enable effect size to be calculated.

2.4. Results

2.4.1. Search Results

Thirty-five papers from 31 studies met the criteria and are included in this review. Search results are shown in Figure 2.1. One doctoral dissertation was excluded, but its related

publication was identified and also excluded [84]. A paper reporting insulin sensitivity data was excluded [85] as this data had been published previously [86] and another paper reporting HbA1c was excluded [87] as this data had been published previously [88]. A paper reporting phase one of a study [82] was excluded due to having a weight loss diet added to the resistance training, however a paper describing phase two [89] was included as dietary modification was ceased at the completion of phase one.

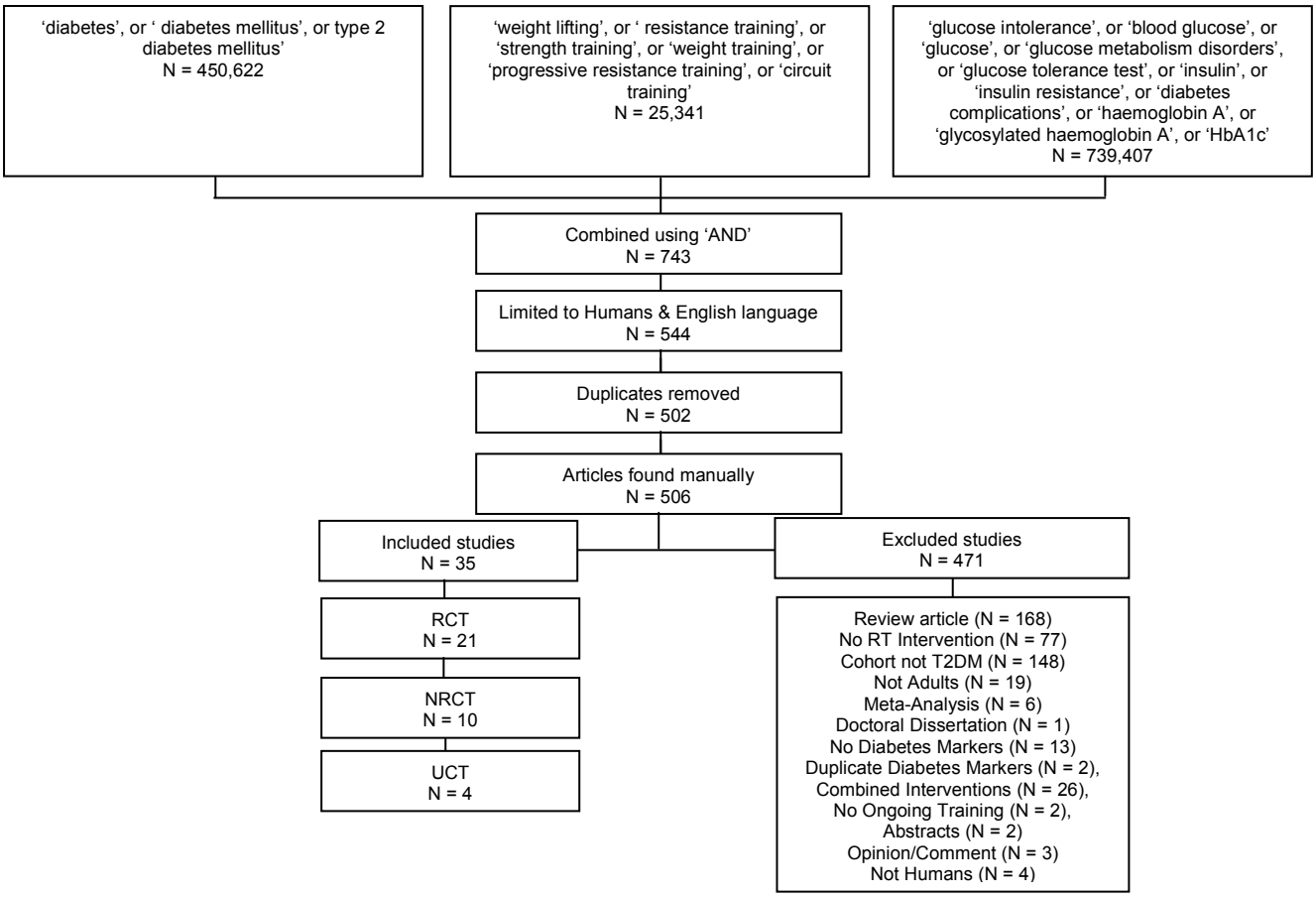

Figure 2.1: Sequence of searching & search results.
RCT = randomised controlled trial; NRCT = non-randomised controlled trial; UCT = uncontrolled trial; RT = resistance training; Combined interventions = aerobic and resistance training OR diet and resistance training.

2.4.1.1. Study Design / Quality Assessment

Most (18/21) of the papers based on randomised controlled trials (RCT) [80, 81, 88, 90-104] reported eligibility criteria (Table 2.1); as did just more than half (8/14) of the trials that had no randomisation.

Assessors were reported to be blinded in only eight papers [81, 88, 91, 99, 103-106]. In all studies, previous medical intervention was maintained with changes to drug regimes occurring only where medically required. With one exception [107], all studies were completed using an out-patient design with participants under free-living conditions.

2.4.1.2. Baseline Characteristics

Generally, there were no differences between intervention and control groups except where studies were intentionally designed to compare different cohorts [62, 63, 86, 108-110] (Table 2.1). Baseline characteristics differed in two RCTs [93, 101] with the resistance training group having higher fasting blood glucose levels and lower body mass index and fat mass than untrained controls [93] and the aerobic group having increased insulin sensitivity compared to the resistance training and control groups [101]. Five studies did not report any analysis between groups at baseline [90, 99, 101, 103, 111].

Table 2.1: **Study Quality**

Reference			Design				Subjects			Intervention			Compliance			Outcome Measures				
	Publication Date	Study Design	Randomization	Concealment	Assessor Blinding	Participant Blinding	Eligibility Criteria	Analysis between groups at baseline	Treatment vs Control similar at baseline	Details of RT exercise prescription	Intensity of RT	Adverse Events Reported	Loss to Follow-up	Attendance	Treatment of missing data specified	Statistical Analysis Specified	Outcomes Identified Primary & Secondary	Sample Size (determined by power calculations	Control & Treatment Method & Analysis the same	CV's Provided
Jorge [100]	2011	RCT	Y	N	N	N	Y	Y	Y	N	N	N	N	Y	N	Y	Y	N	Y	N
Plotnikoff [104]	2010	RCT	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Church [99]	2010	RCT	Y	Y	Y	N	Y	N	?	Y	N	Y	Y	N	N	Y	Y	Y	Y	N
Ku [101]	2010	RCT	Y	N	N	N	Y	N	N	Y	Y	N	N	N	N	Y	N	Y	Y	N
Kwon [102]	2010	RCT	Y	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	N	Y	N
Ng [103]	2010	RCT	Y	Y	Y	N	Y	N	?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Arora [97]	2009	RCT	Y	N	N	N	Y	Y	?	Y	Y	Y	Y	N	N	Y	Y	N	Y	N
Cheung [98]	2009	RCT	Y	N	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	N
Winnick [96]	2008	RCT	Y	N	N	N	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N	Y	N
Baum [90]	2007	RCT	Y	N	N	N	Y	N	?	Y	Y	N	N	N	N	Y	N	N	Y	N
Brooks [91]	2007	RCT	Y	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y
Sigal [88]	2007	RCT	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N
Castaneda [105]	2006	RCT	Y	N	Y	N	N	Y	Y	Y	Y	N	N	N	N	Y	Y	N	Y	Y
Dunstan [94]	2006	RCT	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N
Gordon [95]	2006	RCT	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y
Cauza [92]	2005	RCT	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N
Cauza [93]	2005	RCT	Y	N	N	N	Y	Y	N	Y	Y	Y	N	N	N	Y	Y	N	Y	N
Dunstan [89]	2005	RCT	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y
Baldi [79]	2003	RCT	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y
Castaneda [81]	2002	RCT	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Dunstan [80]	1998	RCT	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y
Bweir [106]	2010	NRCT	N	N	Y	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	N
Hazley [112]	2010	NRCT	N	N	N	N	N	Y	Y	Y	Y	Y	N	Y	N	Y	N	N	Y	N
Ibanez [110]	2008	NRCT	N	N	N	N	Y	Y	N	Y	Y	N	N	Y	N	Y	Y	N	Y	Y
Colberg [108]	2006	NRCT	N	N	N	N	Y	Y	N	Y	Y	N	N	N	N	Y	Y	N	Y	N
Wojtaszewski [109]	2005	NRCT	N	N	N	N	N	Y	N	Y	Y	N	N	N	Y	N	N	N	Y	N
Fenicchia [62]	2004	NRCT	N	N	N	N	Y	Y	N	Y	Y	N	N	N	N	Y	Y	N	Y	N
Holten [86]	2004	NRCT	N	N	N	N	N	Y	N	Y	Y	N	N	N	N	Y	Y	N	Y	N
Ishii [107]	1998	NRCT	N	N	N	N	N	Y	Y	Y	Y	N	N	N	N	Y	Y	N	Y	N
Honkola [111]	1997	NRCT	N	N	N	N	N	N	?	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Smutok [113]	1994	NRCT	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	N	Y	N
Cauza [114]	2009	UCT	N	N/A	N	N	Y	N/A	N/A	Y	N	N	Y	N	Y	Y	Y	N	N/A	N
Misra [115]	2008	UCT	N	N/A	N	N	Y	N/A	N/A	Y	Y	N	N	Y	N	Y	Y	N	N/A	N
Ibanez [116]	2005	UCT	N	N/A	N	N	Y	N/A	N/A	Y	Y	Y	Y	Y	N	Y	Y	N	N/A	Y
Eriksson [117]	1997	UCT	N	N/A	N	N	N	N/A	N/A	Y	Y	Y	N	N	N	Y	Y	N	N/A	N

RCT = Randomised controlled trial; NRCT = non-randomised controlled trial; UCT = uncontrolled trial; ? = not specified; Y = yes; N = no; N/A = not applicable; Adverse events reported = refers to whether the authors reported on adverse events, not that adverse events occurred; CV's provided = coefficient of variation of the measure reported within the methodology section, indicating reliability of the measure.

2.4.1.3. Statistical Analysis and Power Calculations

The purpose of the research was outlined in all studies except six [90, 93, 98, 101, 106, 112], however one paper [109] did not report the purpose despite a previous paper [86] from the same study reporting this information. Additionally, few papers (11/35) reported how missing data were treated (Table 2.1). With the exception of one study [111], the intervention and control groups were subjected to the same research methodology and analysis. Only four studies [88, 99, 101, 104] reported determining sample size by a priori power calculation. Additionally, only seven RCTs reported whether an intention to treat or per protocol design was undertaken [81, 88, 91, 94, 99, 103, 104], with all of these completing an intention to treat design.

2.4.2. Resistance training for type 2 diabetes

Within the included studies, resistance training was almost always completed using machines, including pin-loaded machines (28/35 papers), with some studies incorporating the use of free-weights [62, 80, 92-94, 97, 103, 104, 106, 107, 112-114], however three studies used resistance bands [98, 101, 102] (Table 2.2). Three studies varied the delivery of resistance training using circuit-type training [80, 103, 111]. A whole-body training protocol, mostly progressive in nature where the weight lifted, or sets and repetitions completed increased at varying stages was favoured by most researchers (30/31 studies; Table 2.2). However, one study [86, 109] used only three exercises and focused solely on the lower limbs.

2.4.2.1. Frequency

Resistance training protocols were commonly performed on three non-consecutive days·wk^{-1} (Table 2.2), although one non-randomised study [107] admitted their participants to hospital to complete low intensity resistance training five days·wk^{-1} and two RCTs performed exercises with resistance bands five days·wk^{-1} [98, 101]. Six studies [94, 97, 111, 112, 116, 117] performed resistance training on two days·wk^{-1}, with one study [94] prescribing two days·wk^{-1} to maintain benefits achieved from previously training three days·wk^{-1}. One RCT did not report the frequency of completing resistance training [96].

2.4.2.2. Intensity

The intensity of each resistance training protocol varied considerably, with some studies giving precise information about initial intensities and progression points, while other studies provided vague details of increasing the weight (by an unspecified amount) when participants were able to complete a certain number of sets and repetitions (Table 2.2). Two studies [110, 116] specifically reported completing power exercises using low weight and high velocity movement, in addition to their normal resistance training program. Two studies prescribed the training weight as percentage of one repetition maximum (1RM) but measured strength using 3RM [86, 109], KIN-COM [107] or estimated 1RM from a sub-maximal load, while another study [63] prescribed resistance training based on percentage 10RM after conducting 1RM testing. The precise intensities reported for each RCT are shown in Table 2.2.

2.4.2.3. Duration

The duration of all studies varied from 4-6 weeks to 12 months of training. One study [62] reported the acute effects of resistance training, before also reporting six-week follow-up data. An additional study reported data at six weeks [86, 109], while another study reported a duration of 4-6 weeks [107]. Sixteen studies had durations of 6-16 weeks [79, 80, 96-98, 100-104, 106, 108, 110, 112, 114, 115], and another study examined changes over six months [88] with another over nine months [99]. Additionally, one paper reported a six-month follow-up period [89] after a six month RT and weight loss intervention [82]. One study reported a two-month supervised introductory phase, followed by 12 months of home-based maintenance [94].

Table 2.2: **Exercise intervention characteristics**

Author (year) Country	N = Sample M/F Age y	Control / Comparison condition	Exercise mode & intervention	F: Frequency I: Intensity D: Duration	Strength Test	Resistance Training equipment	Duration	Supervision
Jorge (2011) Brazil [100]	N = 48 CT = 12 RT = 12 AT = 12 C = 12 M = 18/F = 30 53.9 ± 9.9 y	Control: Flexibility exercises 3 times a week Aerobic: 60 min cycling at lactate threshold 3 week^{-1} Combined: Aerobic and resistance at same intensity of corresponding groups but half the volume.	Resistance training: 7 exercises: leg press, bench press, lat pull-down, seated row, shoulder press, abdominal curls & knee curls	F: 3 week^{-1} I: NR D: 60 min	1RM – All exercises	NR	12 weeks	NR
Plotnikoff (2010) Canada [104]	N = 48 RT = 27 C = 21 M = 32/F = 8 54.5 ± 12 y	Non-training control group, no other details specified	Home-based progressive resistance training: 8 exercises: squats, seated row, chest press, shoulder press & 4 others from a group of 9 complementary exercises	F: 3 week^{-1} I: 3 sets x 8-10 reps 70-85% 1RM D: NR	1RM – seated chest press, seated row & leg press	Multigym & dumbbells provided to participant	16 weeks	Qualified exercise specialist for 18 out of 48 sessions
Church (2010) USA [99]	N = 262 CT = 76 AT = 72 RT = 73 C = 41 M = 97/F = 165 55.8 ± 8.7 y	Combined: 150 min of moderate intensity activity per week & 2 week^{-1} RT Aerobic: 150 min of moderate intensity activity per week Control: Weekly stretching & relaxation classes	Resistance training: 9 exercises: bench press, seated row, shoulder press, pull down, leg press, leg extension, leg flexion, abdominal crunches & back extensions	F: 3 week-1 I: 2 sets x 10-12 reps upper body exercises, & abdominal crunches, back extensions; 3 sets x 10-12 reps lower body exercises, D: NR	Biodex	NR	9 months	All sessions: unspecified personnel
Ku (2010) Korea [101]	N = 44 RT = 13 AT = 15 C = 16 M = 0/F = 44 38 – 68 y	Control: Diabetes education, maintain sedentary lifestyle Aerobic: walking 60 min at moderate intensity 5 week^{-1}	Resistance training: elastic banc exercises 3 week^{-1} in hospital gymnasium, 2 week^{-1} at home. Biceps curl, triceps extension, upright row, shoulder chest press, trunk side-bending, seated row, leg press, hip flexion & leg extension.	F: 5 week^{-1} I: 3 sets x 15-20 reps 40-50% max capacity D: NR	1RM – chest and leg press	Resistance bands	12 weeks	Individual supervision

Table 2.2 (continued)

Author (year) Country	N = Sample M/F Age y	Control / Comparison condition	Exercise mode & intervention	F: Frequency I: Intensity D: Duration	Strength Test	Resistance Training equipment	Duration	Supervision
Kwon (2010) Korea [102]	N = 28 RT = 13 C = 15 M = 0/F = 28 56.4±7.1 y	Control: no exercise	Home-based resistance training: 11 exercises: biceps curl, triceps extension, upright rows, shoulder press, chest press, seated row, leg press, hip flexion, leg flexion, leg extension, side bends. 10 minute warm-up and 10 minute cool-down.	F: 3 week^{-1} I: 3 sets x 10-15 reps 40-50% 1RM D: 40 min RT, 60 min total	1RM – chest & leg press	Resistance bands	12 weeks	NR
Ng (2010) Singapore [103]	N = 60 RT = 30 AT = 30 M = 19/F = 41 58 ± 7 y	Aerobic: 50 min at 65-70% of max HR, 2-3 week^{-1}	Progressive resistance training: 9 exercises - circuit: leg press, straight leg raise, hamstrings curl, biceps curl, triceps extension, lateral raises, front raises, hip abduction, hip extension	F: 2-3 week^{-1} I: 3 sets x 10 reps 65-70% 1RM D: 50 min max	Predicted 1RM	Machines and free weights	8 weeks	All sessions physiotherapist
Arora (2009) India [97]	N = 30 RT = 10 AT = 10 C = 10 M = 16/F = 14 40-70 y	Control: no training, maintain medications and diet. Aerobic: walking 30 min 3 week^{-1}	Progressive resistance training: 7 exercises for major muscle groups – biceps, triceps, upper back, abdominals, knee flexors & extensors	F: 2 week^{-1} I: 3 sets of 10 reps 60% 1RM progressing to 100% 1RM D: NR	1RM – exercises not specified	Dumbbells, pulleys, lateral pull down, quadriceps table	8 weeks	NR
Cheung (2009) Australia [98]	N = 40 RT = 21 C = 19 M = 12/ F = 25 60.5 y	Control: no intervention	Home-based resistance training: 7 exercises: chest press, seated back row, leg abduction, leg extension, seated leg press, triceps extension & biceps curl. Plus 5 min warm-up and 5 min cool-down.	F: 5 week^{-1} I: 2 sets x 12 reps D: 30 min RT, 40 min total	Hand grip strength	Resistance bands and body weight	16 weeks	5 sessions by fitness leaders in collaboration with an exercise physiologist
Winnick (2008) USA [96]	N = 59 Whites = 23 RT = 8 AT = 15 African = 36 RT = 12 AT = 24 M = ?/F = ? 25-60 y	White subjects Aerobic: 30-40 min walking on motorised treadmill, 3 week^{-1} for first 4 weeks expending ~600 kcal/week, then 5 week^{-1} expending ~1000 kcal/week.	Progressive resistance training: 8 exercises: not specified, modified after 4 weeks in accordance with performance outcomes.	F: NR I: NR D: NR	10 RM All exercises	Machines	8 weeks	NR

Table 2.2 (continued)

Author (year) Country	N = Sample M/F Age y	Control / Comparison condition	Exercise mode & intervention	F: Frequency I: Intensity D: Duration	Strength Test	Resistance Training equipment	Duration	Supervision
Baum (2007) Germany [90]	N = 40 RT = 13 Flex = 13 Vib = 14 M = 24/F = 16 62.9 ± 7.3 y	Flexibility: 8 exercises, 15 min Vibration: 8 exercises, 20 min	Resistance training 8 whole body exercises: leg extension, seated leg flexion, leg press, seated calf raise, lat pulley, horizontal chest press, butterfly & rowing. Wk 1-6 70% 1RM Wk 7-9 increase to 2 sets x 12 reps, Wk 10-12, 3 sets x 10 reps, 80% 1RM	F: 3 week^{-1} I: 1 set x 12 reps D: 45 min total	1RM, Max isometric torque (quads)	Machine weights	12 weeks	All sessions: Unspecified personnel
Brooks (2007) USA [91]	N = 62 RT = 31 C = 31 M = 40/F = 22 66 ± 15.7 y	Standard type 2 DM care	Resistance training & standard care 5 whole body exercises: upper back, chest press, leg press, knee extension & flexion. Wk 1-8 60-80% 1RM Wk 10-14 70-80% 1RM	F: 3 week^{-1} I: 3 sets x 8 reps High intensity D: 45 min total, 5 min warm-up & cool down	1RM - Upper & lower body	Pneumatic Machine weights	16 weeks	NR
Sigal (2007) Canada [88]	N = 251 RT = 64 AT = 60 CT = 64 C = 63 M = 160/F = 91 54.7 ± 7.5 y	Aerobic: 3 week^{-1} 45 min @ 75% HRmax, Combined: Aerobic & resistance 3 week^{-1} Control: No exercise intervention	Resistance training: 2 groups of 7 whole body exercises: A) Abdominal crunch, seated row, biceps curl, bench press, leg press, shoulder press & leg extension B) Abdominal crunch, lateral pulldown, triceps pushdown, chest press, leg press, upright row & leg curl Progressing from 1 set of 15 reps @ 15RM to 3 sets of 8 reps @ 8RM	F: 3 week^{-1} I: 2-3 sets x 7-9 reps D: NR 2-3 min between sets	8RM	Machine weights	26 weeks	Weekly first 4 weeks, then fortnightly: Unspecified personnel
Castaneda (2006) Germany [105]	N = 18 RT = 13 C = 5 M = 6/F = 12 66 ± 8 y	Standard type 2 DM care	Resistance training 5 whole body progressive exercises: 2 upper body, 3 lower body exercises 60-65% 1RM, increasing to 75-80% 1RM by week 4	F: 3 week^{-1} I: 3 sets x 8 reps Moderate-high intensity D: 45 min total, 5 min warm-up & cool down	1RM - 2 upper & 3 lower body exercises	Pneumatic Machine weights	16 weeks	All sessions: Unspecified personnel

Table 2.2 (continued)

Author (year) Country	N = Sample M/F Age y	Control / Comparison condition	Exercise mode & intervention	F: Frequency I: Intensity D: Duration	Strength Test	Resistance Training equipment	Duration	Supervision
Dunstan (2006) Australia [94]	N = 60 I = 28 C = 29 M = 33/F = 27 60.5 ± 8.2 y	Home based resistance training: given 1 dumbbell & weight plates. Monthly phone call	Community gym based resistance training 8 whole body exercises: similar to program undertaken in a supervised setting previously.	F: 2 week^{-1} I: 3 sets x 8 reps Increase weight when able to perform 3 x 8 D: NR	1RM -Bench press - Leg extension	Machine & free weights	12 months	Yes, YMCA staff
Gordon (2006) USA [95]	N = 30 RT = 15 C = 15 M = 15/F = 15 67 ± 11 y	Standard type 2 DM care: no exercise, fortnightly telephone interview	Resistance training & standard care 5 whole body progressive exercises: knee extension, chest press, leg curl, upper back & leg press. 60-65% 1RM, increasing to 75-80% 1RM by week 4	F: 3 week^{-1} I: 3 sets x 8 reps D: 45 min total, 1-2 min rest between sets, 5 min warm-up	1RM	Pneumatic Machine weights	16 weeks	Yes: Unspecified personnel
Cauza (2005) Austria [92]	N = 43 RT = 22 AT = 17 M = 22/F = 21 56 ± 6.6 y	Aerobic training: cycle 3 week^{-1}, 15 min progressing 5 min per week to 90 min @ 60% VO_{2max}	Resistance training 10 min warm-up moderate cycling Minimal weight wk 1 & 2 to teach technique Progressive resistance from wk 3 10 whole body exercises: bench press, chest cross, shoulder press, pull downs, biceps curls, triceps extensions, situps, leg press, calf raises, leg extensions, increasing to 4, 5 & 6 sets/wk	F: 3 week^{-1} I: 3 sets/wk x 10-15 reps ie. 1 set x 10-15 reps each session Weight increase when able to complete 15 reps D: NR	1RM - bench press - rowing - leg press All seated.	Machine & free weights	4 months	All sessions: Professional instructor, Physician
Cauza (2005) Austria [93]	N = 15 RT = 8 AT = 7 M = 4/F = 11 55 ± 7.8 y	Aerobic training: cycle 3 week^{-1}, 15 min progressing 5 min per week to 90 min @ 60% VO_{2max}	Resistance training 10 min warm-up moderate cycling Minimal weight wk 1 & 2 to teach technique Progressive resistance from wk 3 10 whole body exercises: bench press, chest cross, shoulder press, pull downs, biceps curls, triceps extensions, sit-ups, leg press, calf raises, leg extensions, increasing to 4, 5 & 6 sets	F: 3 week^{-1} I: 3 sets x 10-15 reps Weight increase when able to complete 15 reps D: NR	1RM - seated bench press	Machine & free weights	4 months	All sessions: Professional instructor, Physician

Table 2.2 (continued)

Author (year) Country	N = Sample M/F Age y	Control / Comparison condition	Exercise mode & intervention	F: Frequency I: Intensity D: Duration	Strength Test	Resistance Training equipment	Duration	Supervision
Dunstan (2005) Australia [89]	N = 36 RT=14 C = 12 M = 21/F = 15 60-80 y	Home based flexibility training, 3 week^{-1}, telephoned fortnightly	Home based resistance training 9 whole body exercises: lying dumbbell flies, seated single-leg extension, dumbbell shoulder press, dumbbell bent-over row, standing leg curl, dumbbell biceps curls, dumbbell triceps kickback, abdominal curls. 60-80% 1RM. Additional weights provided to facilitate progression	F: 3 week^{-1} I: 3 sets x 8-10 reps D: NR	1RM	Free weights	6 months	No, telephone monitoring weekly first 4 weeks, then fortnightly
Baldi (2003) New Zealand [79]	N = 18 RT = 9 Con = 9 M = 18/F = 0 47.9 y	No exercise completed.	Resistance training 10 whole body progressive exercises: not specified 1 set x 12 reps in wk 1 then 2 sets x 12 reps. Resistance progressed by 5% when able to successfully complete the program.	F: 3 week^{-1} I: 2 sets x 12 reps Max weight for 10 reps for upper body and 15 reps for lower body exercises. Moderate intensity D: NR, 60 sec rest between sets	Max isokinetic torque - Leg and arm flexion	NR	10 weeks	All sessions: Unspecified personnel
Castaneda (2002) USA [81]	N = 62 RT = 31 C = 31 M = 22/F = 40 66 ± 11.8 y	Standard type 2 DM care: Telephone call fortnightly	Resistance training 5 whole body progressive exercises: chest press, leg press, upper back, knee extension & flexion. Wk 1-8 = 60-80% 1RM Wk 10-14 = 70-80% 1RM Wk 9 & 15 = 10% decrease	F: 3 week^{-1} I: 3 sets x 8 reps High intensity D: 45 min total, 5 min warm-up & cool down	1RM - 2 upper & 3 lower body exercises	Pneumatic Machine weights	16 weeks	All sessions: Unspecified personnel
Dunstan (1998) Australia [80]	N = 27 RT = 15 C = 12 M = 17/F = 10 50 ± 10.4 y	Control: no exercise intervention with medical review fortnightly	Progressive circuit resistance training 10 whole body exercises: leg extension, bench press, leg curl, biceps curls, behind neck pull down, calf raise, overhead press, seated rowing, triceps extension & abdominal curls. Wk 1-2 = 2 sets Wk 3-8 = 3 sets	F: 3 week^{-1} I: 2-3 sets x 10-15 reps D: 60 min total, 30 sec per exercise, 30 sec active rest including warm-up & cool down	1RM - all intervention exercises performed	Machine & free weights	8 weeks	All sessions: Instructor, Physician

RT = resistance training; Flex = flexibility training; Vib = vibration training; 1RM = 1 repetition maximum; min = minutes; Max = maximum; C = control; type 2 DM / T2DM = type 2 diabetes mellitus; standard type 2 DM care = routine medical care for type 2 diabetes mellitus; NR not reported; AT = aerobic training; CT = combined aerobic & resistance training; HRmax = maximum heart rate; wk = week; sec = seconds; YC = young healthy controls; OC = age matched controls; IGT = impaired glucose tolerance; HI = hyperinsulinaemia; HRR = heart rate reserve; VO_{2max} = maximal oxygen uptake; MVC = maximal voluntary contractions

2.4.2.4. Compliance

When the interventions were completed at a specific exercise venue, eight papers reported compliance levels of ≥ 85% with most of the training completed under supervision (Table 2.2). Participants who were given weight equipment [104] or resistance bands [98] and asked to exercise at home achieved 71% and 90% compliance respectively. When direct supervision was removed during maintenance programs at home or at a leisure-centre, adherence dropped to 67-72% [89, 94] and 68% [94] respectively.

2.4.2.5. Adverse Events

Although information regarding adverse events was not reported in 10 of 21 papers reporting RCTs [80, 90, 91, 95, 96, 98, 100-102, 105] and only four of 14 papers describing non-RCTs reported information on adverse events [111, 112, 116, 117] (Table 2.1), the interventions seemed to be well tolerated in these clinical populations with co-morbidities. Cases of hypoglycaemia were reported in five resistance training studies, during training [94], immediately following training [81], during the night after resistance training [93], or at unspecified times, with medication decreased to counteract this outcome [88, 117]. Hypoglycaemic events were also reported with combined training, aerobic training and in the control group, with medication adjusted for this [88]. Additionally, hypoglycaemia occurred frequently in one individual both before and after aerobic training [93], while seven hypoglycaemic events were reported in a control group [81]. In only one case, was hypoglycaemia severe enough to warrant medical attention [94]. Two studies reported musculoskeletal conditions requiring the program to be modified [88, 104], episodes of chest pain were reported twice [81, 88] and one study

reported a case of hypotension [117]. One study reported cases of diverticulitis, lung cancer and cardiovascular events that were unrelated to the exercise programs [99].

2.4.3. Glycaemic Control

2.4.3.1. Glycated Haemoglobin

Glycated haemoglobin (HbA1c) is considered the optimal way of measuring long term (120 days) glycaemic control [118], with HbA1c values of < 7.0% accepted as representing good glucose control [118]. Seventeen RCTs reported HbA1c data (Table 2.3), with two studies [81, 91, 92, 95] reporting HbA1c reduced by 1.0-1.2%, from above 8.0% prior to 16 weeks of moderate-high intensity training. Baldi and Snowling [79] showed an improvement over the intervention period which approached significance ($p = 0.057$) after 10 weeks of resistance training with HbA1c levels reducing from 8.9% to 8.4%. Maintenance programs completed at home [89, 94], or at a community-gym [94] reported glycaemic control returned towards baseline after six months or became worse after 12 months, which is likely to be a result of decreased compliance to the prescribed training. Interestingly, resistance training appears to be as effective as aerobic training at improving HbA1c when compared to control groups [88] and more effective when compared to aerobic training [92]. This finding requires further validation though as the resistance training group appeared to spend a larger volume of time training than the aerobic training group [92]. Sigal and colleagues [88] however, concluded that combined training was superior at improving glycaemic control to either resistance training or aerobic training on their own. The results from these two studies [88, 92] require careful interpretation, given one is a large RCT that was well controlled and conducted over a long duration of six months [88] while the other was smaller and less well controlled

given that only two interventions were prescribed, an aerobic exercise program and a resistance exercise program [92]. The lack of a non-exercising control group limits the ability of Cauza and colleagues [92] to confidently conclude that the changes were absolutely as a result of the exercise interventions, while the lack of comparison between the different exercise interventions within the Sigal and colleagues study [88] draws into question the conclusion the combined training was superior to that of either resistance or aerobic training on their own.

Ten non-RCTs reported HbA1c data, with the trials reporting different subjects (diabetes vs. non-diabetes) indicating significant differences, while in an RCT, both resistance and aerobic exercise caused an improvement to HbA1c which was significantly greater in the resistance training group [106]. Three studies [114, 115, 117] reported an improvement over time, although another [107] reported a 2% improvement in HbA1c which was not statistically significant.

The greatest improvements to glycaemic control occurred when HbA1c was poor (> 8.0%) at baseline however, based on current literature [74], clinically relevant improvements of 0.6% were generally seen with moderate-high intensity resistance training or where the duration of training lasted 10 weeks or longer. The exception to this was 4-6 weeks of low intensity resistance training five days·wk^{-1} resulting in a 2.0% improvement of HbA1c [107], although this study was not randomised and participants were remarkably light and had a low body mass index, reducing the generalisability of this study.

2.4.3.2. Fasting Blood Glucose

Fasting blood glucose is less frequently used as a measure of glycaemic control but can be a substitute when HbA1c is not measured, for instance when the intervention duration is less than that required for a change in glycaemic control to be fully reflected in HbA1c (< 3 months). Twelve RCTs reported fasting blood glucose levels (Table 2.3), with only one [92] reporting a significant change when compared to the comparison group (aerobic). This was quite a large improvement (3.2 $mmol \cdot L^{-1}$) and included some subjects taking insulin, where no other study included subjects taking insulin. This study however was not identically matched in terms of volume, with the resistance training group completing up to six sets of 10-15 repetitions per week for 10 exercises (estimated to be 120 minutes of exercise per week plus 120 minutes of rest/recovery during the sessions) and the aerobic training group completing up to 90 minutes per week. Again, only three [106, 115, 116] of eight [62, 86, 106, 108, 112, 115-117] non-RCTs reporting fasting blood glucose indicated an improvement over time.

2.4.4. Insulin Sensitivity

2.4.4.1. Euglycaemic-Hyperinsulinaemic Clamp

Although considered the gold-standard for determining insulin sensitivity levels [119], only two studies used the euglycaemic-hyperinsulinaemic clamp [86, 107]. Holten and colleagues [86] reported that despite individuals with diabetes having significantly lower glucose disposal rates and therefore greater insulin resistance than controls, leg glucose clearance rates increased during the second stage of the euglycaemic-hyperinsulinaemic clamp, showing that improvements are achievable with resistance training despite being less sensitive to insulin. Ishii and colleagues [107] also used an euglycaemic-

hyperinsulinaemic clamp, reporting a 48% ($p < 0.05$) increase in insulin sensitivity with resistance training and no change in sedentary individuals with diabetes acting as controls.

Comparing these studies is difficult due to one [86] reporting glucose disposal rate at varying levels of insulin infusion, and another [107] reporting final glucose disposal rate. However, it is likely that resistance training for 4-6 weeks will result in increased insulin sensitivity.

2.4.4.2. Oral Glucose Tolerance Test

Insulin sensitivity using area under the curve (AUC) equations for glucose and insulin levels during an oral glucose tolerance test (OGTT) has been validated against the euglycaemic-hyperinsulinaemic clamp [119] with lower glucose values indicating better glucose tolerance and lower insulin values indicating increased insulin sensitivity. The OGTT was used in two RCTs [80, 90] (Table 2.3), with results indicating an improvement in insulin sensitivity when compared to sedentary controls [80] but not when compared to vibration or flexibility training [90], although the method of performing this analysis varied from other studies as blood was drawn from the ear lobe, rather than the commonly used antecubital vein and only glucose was measured, not insulin as well. Two non-RCTs [62, 113] completed OGTTs with AUC for glucose and insulin improving over time with both resistance training and aerobic training [113], although Fenicchia and colleagues [62] showed no change after six weeks of resistance training despite reporting an improvement 12-24 hours after the first resistance training session however, the time of completing the OGTT post training was later. The time utilised for each OGTT trial varied considerably between 24 and 72-96 hours post-

training (Table 2.3). This may be a factor in whether studies reported improvements or not as it is still unclear precisely how long insulin sensitivity remains increased following resistance training, and therefore acute rather than chronic training effects could have been reported. The training regimes may also have contributed to the varied results as different protocols at different intensities were employed by each study.

2.4.4.3. Homeostasis Model Assessment

The homeostasis model assessment (HOMA) is a mathematical model of determining insulin resistance from fasting glucose and insulin concentrations which has been validated against the euglycaemic-hyperinsulinaemic clamp [119]. This was the most common method of determining insulin resistance and estimating insulin sensitivity, possibly because of its ease and speed of completion as it requires only a fasting blood sample, with seven papers describing six RCTs using this method [89, 91, 92, 94-96, 100] (Table 2.3). The HOMA was originally developed in 1985 and updated in 1996 to estimate insulin sensitivity (HOMA2) [120] although it is unclear whether any of the studies using HOMA modelling utilised the updated version.

A reduction in insulin resistance after four months of resistance training ($p = 0.04$) was reported in a study with 22 participants [92], while 12 months of centre-based maintenance following a two-month introductory period saw insulin sensitivity improve ($p < 0.05$) [94]. Comparing resistance training with the control group significantly improved ($p < 0.05$) [91] and tended to improve ($p = 0.08$) [95] insulin resistance, while resistance training compared with aerobic training also showed a trend towards ($p = 0.09$) improvement of insulin resistance [92]. Winnick and colleagues [96] reported a significant improvement in insulin resistance for African Americans completing

resistance training when compared to Whites completing resistance training. There was no difference between ethnicity however, when aerobic training was completed.

Insulin resistance improved by 3.2 units when calculated using HOMA 72 hours after the final session [95], which is supported by a 9.4% improvement in insulin sensitivity when measured 48 hours after the final resistance training session [94]. Additionally two non-RCTs [108, 112] reported HOMA, stating no change in insulin resistance 24 hours and 48-72 hours following the final resistance training session. The limited number of studies and the variation in HOMA limits the ability to make conclusions. However, insulin sensitivity seemed to at least tend to improve compared to a comparison group [80, 91, 92, 95], though how long this improvement remains is unclear.

2.4.4.4. Insulin Sensitivity Index

The insulin sensitivity index is another validated mathematical model for determining insulin sensitivity [119], but was used by only one RCT [79] and one uncontrolled trial [116] with each using a different model. Contrasting results were reported, with Baldi and Snowling [79] finding no evidence of change in either resistance training (10 weeks) or control groups, while Ibanez et al. [116] observed a 46% improvement in insulin sensitivity ($p < 0.001$) after 16 weeks of resistance training. This difference could be time related as the improvement was measured 24 hours after the final session [116] compared to 36-48 hours when no improvement was seen [79], or this could be related to intensity or duration of training.

2.4.4.5. Insulin Tolerance Test

Two RCTs measured insulin sensitivity using an insulin tolerance test [101, 102] and did not report any change over the 12-week resistance training intervention with resistance bands compared to either aerobic or non-exercising controls. One non-RCT [115] used a short insulin tolerance test to measure insulin sensitivity. This test was completed 72-96 hours after the final training session of a 12-week program completed with free weights in a physiotherapy clinic, and reported a significant improvement in insulin sensitivity.

Table 2.3: **Metabolic outcomes**

Author (year) Country	Group	Time of follow up	Type of change	HbA1c (%)	Glucose ($mmol \cdot L^{-1}$)	Insulin ($pmol \cdot L^{-1}$)	Insulin sensitivity method	Insulin sensitivity
Jorge (2011) Brazil [100]	CT	NR	Pre:Post	7.6±1.2:7.5±1.1	8.58±2.35:7.88±2.04		HOMA-IR	3.14±2.12:2.59±1.31
	RT			8.5±2.5:8.2±2.1	10.78±4.41:9.22±3.36			4.54±3.94:4.07±2.90
	AT			7.6±1.7:7.4±1.5	8.14±2.31:7.04±1.99			2.45±1.31:2.24±1.52
	C			6.9±0.7:7.1±0.7	8.26±2.39:6.94±1.14			3.91±4.42:4.28±5.74
			Time effect	NS	$p < 0.05$			NS
Plotnikoff (2010) Canada [104]	RT	NR	Pre:Post	6.9±1.5:7.0±1.4	6.9±2.1:7.1±1.7	92.3±50.1:90.1±46.6		
	C			6.8±0.8:6.8±0.8	7.2±1.4:7.1±1.2	111.2±57.1:137.3±75.3		
			Group effect	$p = 0.27$	$p = 0.59$	$p = 0.02$		
Church (2010) USA [99]	CT	NR	Pre:Post Δ	7.6±0.1:7.4±0.1 -0.2±NR Δ	8.3±2.0:NR NR	173.4±NR:NR NR		
	AT			7.6±0.1:7.4±0.1 -0.1±NR Δ	8.1±1.7:NR NR	111.0± NR:NR NR		
	RT			7.6±0.1:7.5±0.1 0.0±NR Δ	8.5±2.2:NR NR	122.4±NR:NR NR		
	C			7.6±0.1:7.7±0.1 + 0.1±NR Δ	8.8±2.3:NR NR	106.2±NR:NR NR		
			Time effect	NR	NR	NR		
			Group*time	P = 0.03 CT v C NS RT & AT v C	NR	NR		
Ku (2010) Korea [101]	RT	NR	Pre:Post Δ	7.3±0.9:7.0±0.9 -0.3±0.9 Δ	6.3±0.7:7.1±2.2 + 0.8±2.2 Δ		Insulin Tolerance Test – k_{ITT} (%/min)	1.87±0.97:2.13±0.76 + 0.26±1.16 Δ
	AT			7.7±1.0:7.1±0.8 -0.6±1.2 Δ	7.1±1.1:6.7±1.1 -0.4±1.2 Δ			2.81±1.02:2.50±0.63 -0.31±0.93 Δ
	C			7.3±0.7:7.2±0.9 -0.1±0.6 Δ	6.9±1.1:6.7±1.3 -0.2±1.2 Δ			1.98±0.78:2.12±0.62 + 0.14±0.71 Δ
			Group effect	NS	NS			NS

Table 2.3 (continued)

Author (year) Country	Group	Time of follow up	Type of change	HbA1c (%)	Glucose ($mmol \cdot L^{-1}$)	Insulin ($pmol \cdot L^{-1}$)	Insulin sensitivity method	Insulin sensitivity
Kwon (2010) Korea [102]	RT	NR	Pre:Post	7.3±0.9:7.0±0.9			Insulin Tolerance Test – k_{ITT} (%/min)	1.8±1.0:2.1±0.8
	C			7.4±0.7:7.3±0.9				2.0±0.8:2.1±0.6
			Time effect	NS				NS
			Group*time	p = 0.57				p = 0.69
Ng (2010) Singapore [103]	RT	36-48 hours	Pre:Post	8.9±1.5:8.4±1.2	10.4±3.1:10.1±3.6			
			Δ	-0.4±0.6 Δ	-0.3±2.8 Δ			
	AT			8.5±0.9:8.1±1.1	9.5±2.5:9.3±2.2			
				-0.3±0.9 Δ	-0.2±1.7 Δ			
			Group effect	NS	NS			
Arora (2009) India [97]	RT	NR	Pre:Post	7.6±1.4:6.2±0.8				
	AT			8.1±0.9:6.7±0.9				
	C			7.8±0.9:7.4±0.9				
			Time effect	p < 0.05 RT & AT				
			Group effect	NR				
Cheung (2009) Australia [98]	RT	NR	Pre:Post	7.2±1.6:NR				
			Δ	+ 0.3±0.9 Δ				
	C			7.4±1.0:NR				
				-0.1±1.2 Δ				
			Group effect	p = 0.30				

Table 2.3 (continued)

Author (year) Country	Group	Time of follow up	Type of change	HbA1c (%)	Glucose ($mmol \cdot L^{-1}$)	Insulin ($pmol \cdot L^{-1}$)	Insulin sensitivity method	Insulin sensitivity
Winnick (2008) USA [96]	Whites RT	NR	Pre:Post Δ	7.9±2.0:NR			HOMA IR	6.8±4.8:NR +13.2% Δ
	AT			7.8±1.2:NR				10.6±8.5:NR -3.68% Δ
	African RT			6.5±1.0:NR				5.8±2.4:NR -19.15% Δ
	AT			7.6±1.5:NR				8.6±7.4:NR +3.79% Δ
			Time effect	NR				NR
			Group*time	NR				P<0.05 RT African v Whites P>0.05 AT African v Whites
Baum (2007) Germany [90]	RT	72-96 hours	Pre:Post Δ	6.8%±0.17:NR +0.2±0.15 Δ	6.99±1.28:6.66±1.22		OGTT – ear lobe Glucose only	NR:NR -5.6% Δ
	Vib			7.3%±0.66:NR -0.3±0.22 Δ	7.38±3.16:6.77±1.94			NR:NR -6.3% Δ
	Flex			6.7%±0.26:NR +0.34±0.26 Δ	6.66±1.39:6.38±1.22			NR:NR 0.00% Δ
			Time effect	NR	NR			P<0.05 RT & Vib
			Group*time	NR	NR			NR
Brooks (2007) USA [91]	RT	72 hours	Pre:Post Δ	8.7±10.0: 7.6±8.4 -1.0±1.1 Δ	8.8±2.8:7.9±2.2 -0.9±2.8 Δ	116±690:105±390 -16±384 Δ	HOMA-IR	7.1±31.7:5.3±30.6 -0.7±20.0 Δ
	Con			7.8±8.9: 8.3±7.2 +0.4±1.7 Δ	9.9±3.9:9.5±3.3 -0.3±4.5 Δ	115±729:133±702 +6±479 Δ		6.7±50.1:6.4±37.9 +0.8±21.2 Δ
			Time effect	NR	NR	NR		NR
			Group*time	p < 0.001	p = 0.92	p = 0.27		p = 0.05

Table 2.3 (continued)

Author (year) Country	Group	Time of follow up	Type of change	HbA1c (%)	Glucose ($mmol \cdot L^{-1}$)	Insulin ($pmol \cdot L^{-1}$)	Insulin sensitivity method	Insulin sensitivity
Sigal (2007) Canada [88]	RT	Minimum 48 hours	Pre:Post	7.5±1.5:7.2±1.5				
	AT			7.4±1.5:7.0±1.5				
	CT			7.5±1.5:6.6±1.6				
	Con			7.4±1.4:7.5±1.5				
			Time effect	p = 0.018 RT p = 0.002 AT p < 0.001 CT p = 0.57 Con				
			Group*time	p = 0.038 RT v Con p = 0.007 AT v Con p = 0.001 CT v RT p = 0.014 CT v AT				
Dunstan (2006) Australia [94]	Centre	48 hours	Pre:Post Δ	7.8±0.9:NR +0.1±1.0 Δ	9.0±2.0:NR -0.3±1.8 Δ	143.7±66.1:NR -21±47.6 Δ	HOMA	46.9±26.1:NR +9.4±16.4 Δ
	Home			7.5±0.5:NR +0.2±1.2 Δ	8.4±1.9:NR -0.2±2.2 Δ	126.6±55.1:NR -8.5±32.8 Δ		50.7±24.6:NR +2.4±12.4 Δ
			Time effect	p < 0.05 both grps	NS	p < 0.05 centre		p < 0.05 centre
			Group*time	NS	NS	NS		NS
Gordon (2006) USA [95]	RT	72 hours	Pre:Post	8.7±1.9:7.7±1.6		173±108:132±54	HOMA-IR	8.5±27.9:5.3±24.4
	Con			8.0±1.6:8.3±1.6		157±101:168±139		6.7±30.2:7.1±28.7
			Time effect	NR		NR		NR
			Group*time	p < 0.01		p < 0.05		p = 0.08

Table 2.3 (continued)

Author (year) Country	Group	Time of follow up	Type of change	HbA1c (%)	Glucose ($mmol \cdot L^{-1}$)	Insulin ($pmol \cdot L^{-1}$)	Insulin sensitivity method	Insulin sensitivity
Cauza (2005) Austria [92]	RT	NR	Pre:Post Δ	8.3±8.0:7.1±1.7 -1.2 Δ	11.32±7.62:8.16±3.77 -3.2 Δ	130.9±84.0:118.4±85.4 -12.5 Δ	HOMA-IR	9.1±7.0:7.2±5.6 -2.0 Δ
	AT			7.7±1.2:7.4±1.2 -0.3Δ	8.88±2.06:8.83±2.31 -0.05 Δ	105.1±77.5:125.6±96.1 +20.46 Δ		6.8±5.8:8.4±7.8 +1.5 Δ
			Time effect	p = 0.001 RT; NS AT	p < 0.001 RT; NS AT	NS both grps		p = 0.04 RT; NS AT
			Group*time	p = 0.009	p = 0.002	p = 0.04		p = 0.009
Cauza (2005) Austria [93]	RT	NR	Pre:Post	7.5±1.4:7.0±2.1				
	AT			8.0±3.8:7.6±4.8				
			Time effect	NS both groups				
			Group*time	NR				
Dunstan (2005) Australia [89]	RT	48 hours	Pre:post Δ	Returned toward baseline	NR:NR +0.3±2.2 Δ	NR:NR -0.1±46.8 Δ	HOMA-IR	NR:NR +0.04±5.5 Δ
	Con			Returned toward baseline	NR:NR -0.5±2.1 Δ	NR:NR -19.3±50.1 Δ		NR:NR +5.4±6.5 Δ
			Time effect	p < 0.05	NS both grps	p < 0.05 Con; NS RT		p < 0.05 Con; NS RT
			Group*time	NR	NS	NS		NS
Baldi (2003) New Zealand [79]	RT	36-48 hours	Pre:Post	8.9±3.6:8.4±1.8	12.0±2.7:11.4±2.4	268.1±106.3:146.5±85.4	Insulin sensitivity index 0,120	20.3±3.9:22.6±3.9
	Con			8.5±2.4:8.4±1.8	11.1±3.3:11.0±3.0	191.7±191.7:214.6±156.3		22.2±11.4:19.9±5.1
			Time effect	p = 0.057 RT; 0.64 Con	p < 0.05 RT	p < 0.05 RT		NS
			Group*time	NR	NR	NR		NR
Castaneda (2002) USA [81]	PRT	48 hours	Pre:Post Δ	8.7±1.7:7.6±1.1 -12.6±11.1% Δ	8.8±2.8:7.9±2.2			
	Con			8.4±1.7:8.3±2.8 +1.2±5.6% Δ	9.7±3.9:8.9±3.9			
			Time effect	NR	NR			
			Group*time	p = 0.01	p = 0.34			

Table 2.3 (continued)

Author (year) Country	Group	Time of follow up	Type of change	HbA1c (%)	Glucose ($mmol \cdot L^{-1}$)	Insulin ($pmol \cdot L^{-1}$)	Insulin sensitivity method	Insulin sensitivity
.Dunstan (1998) Australia [80]	CRT	48 hours	Pre:Post Δ	8.2±1.9:8.0±1.9	9.6±3.5:9.4±3.1	64.3±49.1:63.1±48.8	OGTT - Glucose AUC - Insulin AUC	-22±240 Δ -2183±6053 Δ
	Con			8.1±2.1:8.3±2.4	9.9±4.2:9.8±4.5	82.6±36.4:93.8±43.7		+191±291 Δ +3947±5352 Δ
			Time effect	NS both grps	NS both grps	NS both grps		NR
			Group*time	NS	NS	NS		$p < 0.05$ glucose & insulin

RT = resistance training; Flex = flexibility training; Vib = vibration training; Con = control; T2DM = type 2 diabetes mellitus; NR = not reported; AT = aerobic training; YC = young healthy controls; OC = age matched controls; grps = groups; NS = not significant; PRT = progressive resistance training; CRT = circuit resistance training; CT = combined aerobic & resistance training

Castaneda [105] did not report any metabolic variables

2.4.5. Insulin Signalling

Only three studies reported data on glucose transport and insulin signalling in individuals with diabetes [86, 100, 105, 109] with two of these being RCTs [100, 105]. Improved glucose disposal, as measured by incorporation into muscle glycogen, support findings using the euglycaemic-hyperinsulinaemic clamp [86, 105]. Changes in the glucose transporter-4 (GLUT4) are less clear with an earlier study [86] reporting a 40% increase ($p < 0.05$) in GLUT4 density compared to a more recent study [105] reporting no evidence of change in GLUT4 gene or protein expression. This could be due to population differences (males vs. females) or the different training protocols (whole-body vs. lower-limb).

Eight weeks of moderate-high intensity resistance training resulted in increased protein content of the insulin receptor, protein kinase-B, and glycogen synthase to similar levels in individuals with diabetes and healthy control subjects [86]. However, no training effect was observed for protein content of insulin receptor substrate-1, the p85 subunit of phosphatidylinositol(PI)-3-kinase, or percent glycogen synthase activity [86]. This is in contrast to findings from 12 weeks of resistance training and combined aerobic and resistance training that produced increased expression of insulin receptor substrate-1 [100]. Moderate-intensity resistance training resulted in similar changes to various AMP-activated protein kinase (AMPK) subunit isoforms (α1:+16%, β2:+14%, γ1:+29%, γ3:-48%) in patients with diabetes and healthy controls [109], while muscle glycogen levels significantly increased with resistance training [86, 105], when compared to controls ($p = 0.04$) [105].

2.4.6. Muscle Strength

Fifteen papers from 12 RCTs reported muscle strength data (Table 2.4), with all but three studies [94, 98, 99] reporting statistically significant improvements after completing resistance training. One of these studies [94] actually reported a decrease ($p < 0.05$) in strength after resistance training, with small losses after 12 months of a home or leisure-centre based maintenance program following on from a two-month supervised intervention period, although only lower body strength in the home-based group decreased below baseline, and was likely to be due to not being able to maintain the appropriate intensity. In most cases [81, 89, 91, 101, 102, 104, 105], these changes were significant when compared to sedentary controls, but not when compared to aerobic training [92, 93]. Eight non-RCTs [62, 86, 107, 108, 110, 113, 114, 116] also reported muscle strength improved, with similar improvements in muscle strength observed in individuals with diabetes compared to those without diabetes [86, 108]. One study also reported muscle power output improved over time [110]. Studies that reported greater improvements in muscular strength, utilised durations between 16 weeks [92, 93, 114, 116] and six months [89] at moderate or moderate-high intensities. In contrast to other results, one study [62] reported highly significant ($p < 0.01$) increases in muscle strength after six weeks of moderate intensity resistance training and two studies reported significant changes in strength against control groups with 12 weeks of training with resistance bands [101, 102]. However, overall it appears that higher intensity resistance training is appropriate and more time efficient for muscle strength gains, although data evaluating lower intensity resistance training in patients with diabetes is limited (4/31 studies).

Improved glycaemic control was observed in five [79, 81, 91, 92, 95] of the 13 papers from RCTs (3 studies) that reported significant improvements in strength, while four RCTs [80, 90-92, 95] that increased strength also improved insulin sensitivity, leaving five RCTs [79, 89, 101, 102, 104] that did not improve insulin sensitivity despite increasing strength. In non-RCTs, one study that improved strength reported improved glycaemic control [114], while four studies [86, 107, 113, 116] that improved strength reported improved insulin sensitivity and two [62, 108] did not improve insulin sensitivity.

2.4.7. Body Composition

2.4.7.1. Lean Body Mass

Lean body mass was measured by dual energy x-ray absorptiometry (DXA) in eight studies [81, 89, 91, 99, 101, 102, 104, 107, 115] including six RCTs [81, 89, 91, 99, 101, 102, 104], or estimated after accounting for fat mass in a further seven studies [62, 63, 79, 88, 92, 94, 113, 114] including four RCTs [79, 88, 92, 94], with one study [93] not specifying the method used (Table 2.4). Results varied, with significant lean body mass increases of 1kg [102] and 3-6kg with resistance training [79, 92, 93] and 2kg with aerobic training [93]. Three studies reported significant ($p < 0.05$; $p = 0.04$) [81, 91, 102] or a trend ($p < 0.08$) [89] towards improvements for lean body mass when resistance training was compared with the non-exercising control group.

2.4.7.2. Fat Mass

Fat mass was typically determined through mathematical equations after measuring body mass and using various techniques to estimate percentage fat. Significant decreases in fat

mass of 1-4.5kg with resistance training [62, 89, 92, 93, 102, 114, 116] and 2kg with aerobic training [92, 93] occurred over the training duration (Table 2.4). One study [79] reported no changes in fat mass with resistance training, compared with a 3.5kg increase ($p < 0.05$) in controls over 10 weeks. With the exception of one study [62], interventions with durations less than 10 weeks did not report fat mass (Table 2.4). The current evidence suggests that moderate or high intensity training of greater than 10 weeks tends to reduce fat mass in individuals with type 2 diabetes.

2.4.7.3. Percentage Body Fat

One non-RCT [107] reported a decrease in percentage body fat as measured by DXA. With two RCTs [96, 104] and one non-RCT [115] reporting no change. Percentage body fat results were not reported in other studies despite utilising DXA [81, 89, 91, 99, 101, 102]. Two further studies [79, 113] utilised hydrostatic weighing, and reported no evidence of change to percentage body fat (Table 2.4). Bioelectrical impedance was used in three studies [62, 88, 94, 103], with changes only reported when aerobic training was compared to controls ($p = 0.008$) [88] (Table 2.4). Four studies utilised the less sensitive measure of skin-fold measurements where decreases in body fat of up to 9.1% were reported (Table 2.4). One non-RCT [110] reported percentage body fat results, but not how it was measured.

2.4.7.4. Body Mass

Typically there was no change in body mass with any exercise regimen; however, one study [79] reported a 2kg increase ($p < 0.05$) after 10 weeks of moderate intensity resistance training (Table 2.4). After six months of home-based maintenance [89], body

mass significantly increased ($p < 0.05$), although final levels remained lower than baseline.

2.4.7.5. Girth Measures

Measures of waist circumference were not routinely completed (14/31 studies; Table 2.4) [62, 81, 88, 89, 91, 94, 95, 98, 99, 101-104, 115, 117, 121] with change occurring when comparing sedentary controls with resistance training [81], aerobic training [88, 103] and over time with resistance training [89, 102, 112, 115]. Waist circumference was reported to remain decreased after six months of home-based resistance training maintenance [89]

.

Table 2.4: Body composition markers

Author(year) Country	Group	Type of change	Mass (kg)	BMI (kg.m^{-2})	Waist Circumference (cm)	Muscle Strength (kg) unless specified	% fat method	% fat	Fat Mass (kg) Unless specified	LBM (kg)
Jorge (2011) Brazil [100]	CT	Pre:Post		31.2±3.9:31.1±3.5						
	RT			32.1±3.8:30.8±5.0						
	AT			29.3±2.2:29.1±2.4						
	C			30.0±4.9:30.1±4.8						
		Time effect		NS						
Plotnikoff (2010) Canada [104]	RT	Pre:Post	97.2±27.1:97.8±27.3	35.3±8.5:35.6±9.0	110.0±16.6:108.6±16.8	46.2±21.8:55.5±26.3^ 128.1±86.0:175.0±141.5∨	DXA	41.9±6.7:42.0±6.8	35.6±7.8:35.6±9.0	50.1±12.7:49.9±12.9
	C		100.5±18.4:100.2±20.4	35.9±5.2:35.9±5.8	115.4±14.1:114.7±15.6	44.9±15.8:44.8±15.9 99.5±61.5:93.8±63.4		41.5±7.4:41.4±7.2	38.5±8.5:37.8±7.9	55.0±12.7:54.3±12.6
		Group effect	p = 0.41	p = 0.59	p = 0.64	p = 0.003		p = 0.71	p = 0.31	p= 0.59
Church (2010) USA [99]	CT	Pre:Post Δ	100.6±20.4:NR -1.5±NR Δ	35.8±6.2:NR NR	114.9±14.5:NR -2.8±NR Δ	2.2±0.6:NR (Nm.kg^{-1}) +0.2±NR Δ	DXA	38.8±6.8:NR NR	39.0±11.3:NR -1.7±NR	57.9±11.3:NR 0.0±NR
	AT		97.5±18.6:NR -0.8±NR Δ	34.7±6.1:NR NR	111.3±14.2:NR -1.5±NR Δ	2.3±0.6:NR -0.1±NR Δ		37.1±7.7:NR NR	35.7±10.1:NR -0.6±NR	57.3±10.7:NR -0.5±NR
	RT		96.9±16.6:NR -0.3±NR Δ	34.1±5.4:NR NR	110.9±12.2:NR -1.9±NR Δ	2.2±0.6:NR +0.2±NR Δ		37.0±7.6:NR NR	36.1±10.1:NR -1.4±NR	58.2±10.7:NR +0.8±NR
	C		97.0±20.0:NR +0.4±NR Δ	34.8±6.2:NR NR	110.6±14.4:NR +0.7±NR Δ	2.1±0.5:NR 0.00±NR Δ		38.5±7.0:NR NR	37.9±11.8:NR +0.1±NR	56.9±11.8:NR +0.1±NR
		Time effect	NR	NR	NR	NR		NR	NR	NR
		Group*time	NR	NR	NR	NR		NR	NR	NR
Ku (2010) Korea [101]	RT	Pre:Post	66.1±4.4:65.0±4.7 -1.1±1.3 Δ	27.1±2.3:26.7±2.3 -0.4±0.5 Δ	90±5:88±6 -2±3 Δ	17±4:19±4^ +2±2 Δ 87±25:97±15∨ +10±16 Δ	DXA	NR	NR	NR
	AT		66.3±6.0:64.4±5.4 -1.9±1.2 Δ	27.1±2.4:26.3±2.1 -0.8±0.5 Δ	89±5:86±5 -3±3 Δ	17±3:15±3^ -2±3 Δ 89±23:82±25∨ -7±22 Δ		NR	NR	NR
	C		67.6±7.5:67.0±7.4 -0.6±1.7 Δ	27.4±2.8:27.1±2.8 -0.3±0.7 Δ	90±12:90±6 0±14 Δ	18±6:16±7^ -2±2 Δ 87±33:75±24∨ -12±21 Δ		NR	NR	NR
		Group effect	p = 0.05	p = 0.04	NS	P < 0.001^; = 0.004∨				

Table 2.4 (continued)

Author(year) Country	Group	Type of change	Mass (kg)	BMI (kg.m^{-2})	Waist Circumference (cm)	Muscle Strength (kg) unless specified	% fat method	% fat	Fat Mass (kg) Unless specified	LBM (kg)
Kwon (2010) Korea [102]	RT	Pre:Post	66.1±4.4:65.0±4.7	27.1±2.2:26.7±2.2	90.2±5.0:87.9±5.6	16.5±4.3:18.5±4.4^ 86.8±24.8:96.9±15.1∨	DXA		23.1±4.5:21.3±4.6	40.3±3.4:41.5±4.1
	C		68.2±7.5:67.5±7.3	27.6±2.8:27.3±2.8	89.8±12.5:89.3±5.7	18.1±6.6:17.0±6.7^ 85.7±33.1:75.1±24.1∨			24.7±5.1:24.0±51.9	41.2±5.0:41.1±4.8
		Time effect	p = 0.009 RT; NS C	p = 0.008 RT; NS C	p = 0.009 RT; NS C	p < 0.05 All			p < 0.001 RT; = 0.02 C	p = 0.003 RT; NS C
		Group*time	p = 0.42	p = 0.52	p = 0.49	p < 0.001^; = 0.006			p = 0.04	p = 0.007
Ng (2010) Singapore [103]	RT	Pre:Post Δ	69.5±14.2:69.7±14.4 +0.2±1.1 Δ	27.4±4.7:27.5±4.7 +0.1±0.4 Δ	90.8±11.2:89.2±11.7 -1.6±2.6 Δ		Bio-impedance	33.1±6.2:31.6±6.1 -1.4±2.4 Δ		
	AT		70.3±13.8:70.2±13.6 0.0±1.4 Δ	27.8±5.2:27.8±5.2 0.0±0.5 Δ	91.9±11.6:92.1±11.0 +0.2±2.4 Δ			33.9±5.2:32.8±5.3 -1.1±2.2 Δ		
		Group effect	NS	NS	p < 0.05			NS		
Arora (2009) India [97]	RT	Pre:Post		27.0±4.1:26.8±4.1						
	AT			26.2±3.2:25.8±3.8						
	C			25.0±3.0:25.1±3.1						
		Time effect		NS						
		Group effect		NR						
Cheung (2009) Australia [98]	RT	Pre:Post Δ		39.7±9.0:NR -0.2±1.2 Δ	126.1±19.2:NR -3.3±6.7 Δ	25.3±10.3:NR – Left +1.0±5.9 Δ 26.4±10.9:NR – Right +1.6±4.6 Δ				
	C			37.7±9.2:NR +0.3±1.0 Δ	121.4±20.5:NR -0.3±4.4 Δ	25.7±9.8:NR – Left -0.5±3.5 Δ 26.6±10.7:NR – Right +0.2±2.7 Δ				
		Group effect		p = 0.22	p = 0.12	p = 0.40 – Left p = 0.26 - Right				

Table 2.4 (continued)

Author(year) Country	Group	Type of change	Mass (kg)	BMI (kg.m^{-2})	Waist Circumference (cm)	Muscle Strength (kg) unless specified	% fat method	% fat	Fat Mass (kg) Unless specified	LBM (kg)
Winnick (2008) USA [96]	Whites RT	Pre:Post					DXA			
		Δ	98.1±20.1:NR	35.1±5.7:NR +2.6% Δ				40.2±12.5:NR +1.38% Δ		
	AT		99.1±23.6:NR	36.5±6.6:NR -1.18% Δ				38.6±9.3:NR -0.22% Δ		
	African RT		109.5±39.5:NR	33.6±5.9:NR -2.6% Δ				38.5±11.4:NR -0.85% Δ		
	AT		99.5±17.2:NR	34.2±5.9:NR -0.7% Δ				38.3±9.8:NR -0.40% Δ		
		Time effect	NR	NR				NR		
		Group*time	NR	p < 0.05 RT African v Whites				NS		
Baum (2007) Germany [90]	RT	Pre:Post	86.5±14.7:NR			NR:NR (Nm.kg^{-1})				
		Δ	-1.30±2.36 Δ			+14% Δ (left leg)				
	Vib		83.3±13.4:NR - 0.86±1.77 Δ			NR:NR NR Δ				
	Flex		88.6±24.1:NR -1.68±4.57 Δ			NR:NR NR Δ				
		Time effect	NS			NR				
		Grp*time	NR			NR				
Brooks (2007) USA [91]	RT	Pre:Post		30.9±6.13:NR	99.7±12.81:NR	66±22:90±33^	DXA		35.0±12.25:NR	44.3±9.5:45.5±10.6
		Δ		NR Δ	NR Δ	+24±11 Δ 338±150:568±189∨ +173±106 Δ			NR Δ	+1.1±1.67 Δ
	Con			31.1±5.57:NR NR Δ	100.1±14.48:NR NR Δ	62±22:58±22^ -4±11 Δ 300±156:285±150∨ -19±39 Δ			33.7±13.36:NR NR Δ	44.9±10.6:44.8±9.5 +0.4±1.11 Δ
		Time effect		NR	NR	NR			NR	NR
		Group*time		NR	NR	p < 0.001			NR	p = 0.04

Table 2.4 (continued)

Author(year) Country	Group	Type of change	Mass (kg)	BMI (kg.m^{-2})	Waist Circumference (cm)	Muscle Strength (kg) unless specified	% fat method	% fat	Fat Mass (kg) Unless specified	LBM (kg)
Sigal (2007) Canada [88]	RT	Pre:Post	99.1±30.4:98.0±30.4	34.1±9.6:33.7±9.6	110±24:107±24		Bioelectrical impedance	35.9±9.6:35.0±9.6	36.5±19.2:35.2±19.2	62.3±13.6:62.5±13.6
	AT		103.5±31.0:100.9±30.2	35.6±10.1:34.8±10.1	113±23:110±23			37.0±9.3:36.3±9.3	39.2±19.4:37.6±19.4	64.0±13.9:63.0±13.9
	CT		101.9±30.4:99.3±30.4	35.0±9.6:34.2±9.6	112±24:108±24			36.0±9.6:35.0±9.6	37.6±19.2:35.7±19.2	63.9±13.6:63.2±13.6
	Con		101.3±28.6:101.0±27.8	35.0±9.5:34.9±8.7	112±24:111±24			36.6±8.7:36.9±9.5	38.0±17.5:38.2±17.5	63.0±12.7:62.5±12.7
		Time effect	NR	NR	NR			NR	NR	NR
		Group*time	p = 0.008 AT v Con	p = 0.009 AT v Con	p = 0.03 AT v Con			NS	p = 0.44 AT v Con	NS
Castaneda (2006) Germany [105]	RT	Pre:Post		32.1±6.8:NR NR Δ		NR:NR +43±29% Δ*				
	Con			33.4±6.3:NR NR Δ		NR:NR +19±31% Δ*				
		Time effect		NR		NR				
		Group*time		NR		p = 0.01				
Dunstan (2006) Australia [94]	Cent	Pre:Post Δ	92.6±17.1:NR -2.1±3.4 Δ	32.8±4.8:NR NR Δ	105.6±11.7:NR -1.3±5.3 Δ	78.8±43.9:NR^ -3.4±17.8 Δ 29.9±10.1:NR∨ -7.2±10.5 Δ	Bioelectrical impedance		37.6±12.3:NR -0.8±3.2 Δ	55.0±9.8:NR -1.3±1.6 Δ
	Home		91.2±13.6:NR -2.2±3.2 Δ	32.4±4.4:NR NR Δ	107.4±10.8:NR -2.0±5.9 Δ	78.3±49.1:NR^ -3.7±19.6 30.3±12.0:NR∨ -0.3±6.3 Δ			35.8±10.0:NR -1.0±3.2 Δ	55.4±10.5:NR -0.9±2.2 Δ
		Time effect	p < 0.05 both grps	NR	NS	p < 0.05 RT∨			NS	p < 0.05 both grps
		Group*time	NS	NR	NS	p < 0.05 ∨			NS	NS
Gordon (2006) USA [95]	RT	Pre:Post	80±19:NR	30.7±6.2:31.3±6.2	100±13.4:101±10.8					
	Con		88±15:NR	33.5±6.2:33.4±5.8	108±11.2:109±12.4					
		Time effect	NR	NR	NR					
		Group*time	NR	p = 0.05	p = 0.43					

Table 2.4 (continued)

Author(year) Country	Group	Type of change	Mass (kg)	BMI (kg.m^{-2})	Waist Circumference (cm)	Muscle Strength (kg) unless specified	% fat method	% fat	Fat Mass (kg) Unless specified	LBM (kg)
Cauza (2005) Austria [92]	RT	Pre:Post Δ	91.3±13.6:90.2±13.1 -1.1% Δ	31.3±4.2:30.9±4.2 -1.1% Δ		54.6±16.0:68.6±18.8^ +26% Δ 114±36.6:168±45.5∨ +48% Δ	10 site skinfolds	44.5±3.8:40.5±5.2 -9.1% Δ	39.6±6.6:35.8±8.0 -9.7% Δ	49.4±8.4:52.6±8.0 +6.5% Δ
	AT		96.7±18.6:95.4±18.6 -1.1% Δ	33.9±5.4:33.5±5.4 -1.1% Δ		43.9±15.7:45.0±16.1^ +2.5% Δ 93±35.9:107±42.1∨ +15% Δ		46.3±3.3:44.5±3.3 -3.4% Δ	44.8±9.5:42.5±8.7 -5.3% Δ	51.9±10.3:52.9±11.1 +2% Δ
		Time effect	NS	NS		p < 0.001 RT^∨; ET∨		p < 0.001 both grps	p < 0.001 both grps	p < 0.001 RT
		Group*time	NR	NR		NR		NR	NR	NR
Cauza (2005) Austria [93]	RT	Pre:Post		29.9±2.3:29.9±2.8		47.4±15.0:59.7±18.4^	NR		38.9±6.5:33.5±7.9	46.3±7.4:51.9±9.1
	AT			36.3±12.4:36.3±6.9		31.8±10.6:31.7±10.6^			46.9±10.6:44.4±10.3	56±10.3:58.2±11.1
		Time effect		NS		p = 0.01 RT; NS AT			p < 0.01 both grps	p < 0.01RT; = 0.03AT
		Group*time		p = 0.03		NR			p = 0.04	NR
Dunstan (2005) Australia [89]	RT	Pre:Post Δ	88.7±10.9:NR unspecified increase		NR:NR -3.4±4.7 Δ	NR:NR +26.4±22.8^ Δ +4.9±6.4∨ Δ	DXA		33.1±7.4:NR NR Δ	51.8±8.1:NR NR Δ
	Con		89.5±12.1:NR unspecified increase		NR:NR -2.0±4.3 Δ	NR:NR -0.2±19.1^ Δ -0.1±5.4∨ Δ			35.6±6.8:NR NR Δ	49.7±9.5:NR NR Δ
		Time effect	p < 0.05 RT		p < 0.05 RT	p < 0.05 RT^∨			p < 0.01 both grps	NS
		Group*time	NR		NS	p < 0.05^∨			NR	p < 0.08
Baldi (2003) New Zealand [79]	RT	Pre:Post Δ	112.3±12.0:114.0±12.3	34.3±9.6:NR		NR/NR:NR/NR(ext/flx) +32.0/+3.2%^ Δ +18.1%/+37.0%∨ Δ	Hydrostatic weighing	32.4±3.3:NR	38.1±10.5:37.0±10.5	74.3±3.6:76.9±3.3
	Con		110.3±21.9:110.9±22.2	36.4±9.3:NR		NR/NR:NR/NR NR/NR Δ		30.7±6.6:NR	37.7±17.1:40.3±18.9	72.6±9.6:70.6±9.0
		Time effect	p < 0.05 RT, NS Con	NR		p < 0.05 RT^∨		NR	p < 0.05 Con	p < 0.05 RT; NS Con
		Group*time	NR	NR		NR		NR	NR	NR

Table 2.4 (continued)

Author(year) Country	Group	Type of change	Mass (kg)	BMI (kg.m^{-2})	Waist Circumference (cm)	Muscle Strength (kg) unless specified	% fat method	% fat	Fat Mass (kg) Unless specified	LBM (kg)
Castaneda (2002) USA [81]	PRT	Pre:Post Δ	79.3±17.8:79.5±18.4		99.7±12.8:97.5±12.8	389±167:518±267* +33±7% Δ	DXA		35.0±12.3:34.0±12.8	44.3±9.5:45.5±10.6
	Con		78.6±17.3:79.4±16.2		100±14.5:102±12.3	351±173:299±167* -15±3% Δ			33.7±13.4:34.6±12.3	44.9±10.6:44.8±9.5
		Time effect	NR		NR	NR			NR	NR
		Group*time	p = 0.89		p = 0.07	p = 0.0001			p = 0.26	p = 0.04
Dunstan (1998) Australia [80]	CRT	Pre:Post Δ	83.6±14.3:83.2±14.3	28.3±3.1:28.1±3.1		NR:NR +15±6%^ Δ +43±12%∨ Δ	7 site skinfolds	NR	NR	NR
	Con		82.7±12.8:83.7±13.2	30.1±3.8:30.4±3.8		NR:NR NR^∨ Δ				
		Time effect	NR	NR		p < 0.05^∨				
		Group*time	p < 0.05	p < 0.05		NR				

RT = resistance training; Flex = flexibility training; Vib = vibration training; Con = control; Cent = centre based training; T2DM = type 2 diabetes mellitus; AT = aerobic training; YC = young healthy controls; OC = age matched controls; grps = groups; NS = not significant; PRT = progressive resistance training; CRT = circuit resistance training; ^ = upper body; ∨ = lower body; * = whole-body; ext = extension; flx = flexion; CT = combined aerobic & resistance training; NR = not reported

2.4.8. Cardiac Risk Factors

2.4.8.1. Lipid Profile

Blood lipids were reported in 14 studies with general improvements in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides reported after resistance training ($p < 0.001$; $p < 0.01$; $p < 0.05$) [92, 97, 100, 111, 115].

2.4.8.2. Blood Pressure

Blood pressure was measured in 16 studies. Three studies reported positive changes in systolic blood pressure associated with all forms of training [81, 90, 92, 97, 100, 103, 114]. Improvements to diastolic blood pressure were less frequently observed, but still occurred over time with resistance training, aerobic training and combined exercise [92, 100, 114].

2.5. Discussion

Individuals with T2D are able to complete resistance training with minimal risk of negative health outcomes or injury, while improving overall glycaemic control, insulin sensitivity and muscular strength. Overall, based on reporting the criteria outlined within the CONSORT statement [122], the quality of the study design was good with 21 papers reporting on 18 RCTs, of which 10 were published between 2005 and 2008 and eight were published between 2009 and 2011. The major findings from these studies are that completing resistance training, and aerobic training over extended durations will result in similar improvements to glycaemic control [88, 93, 97, 101, 103]. However, resistance training could potentially provide greater benefits in terms of glycaemic control than aerobic training with researchers and practitioners intimating that resistance training,

comprising short bouts with intermittent rest periods, provides an attractive alternative to aerobic training [77, 123, 124]. Further investigation into the ability to complete each exercise mode is required though as data reported from exercise interventions indicates little difference in adherence to the different exercise modes [88]. Whether this is the same in real life clinical scenario's is currently unknown. To further improve the quality of studies and knowledge in this area and to enable comprehensive comparison between studies in the future, consideration needs to be given to quantifiable and replicable exercise prescriptions, specifying how missing data is treated and determining sample sizes by power calculations.

A clinically relevant lowering of HbA1c, a key marker of improved long term glycaemic control, was reported in a number of resistance training studies whilst those reporting no effect were intervention studies with durations of 12 weeks or less. These changes appear to be of a similar or greater magnitude to aerobic training [88, 92, 93, 97, 101, 103], however the effect of combining resistance with aerobic training remains unclear with only three studies [88, 99, 100] making a direct comparison between combined training and isolated resistance or aerobic training interventions.

Interestingly, insulin sensitivity was only evaluated using the euglycaemic-hyperinsulinaemic clamp in non-RCTs [86, 107]. Both of these studies reported increased insulin sensitivity following resistance training, despite the time that the measure was performed varying from 16 to 48 hours following the final exercise session and the intensity and frequency of the training varying markedly. Other, less precise measures of insulin sensitivity, generally indicated improvements at times ranging from 24 to 72-96 hours [90, 115] following the final resistance training session of a long-term training

program. However, the effect of a single session of resistance training on insulin sensitivity in previously untrained subjects has not been investigated beyond 12-24 hours after the session [62, 63]. This raises questions about the training frequency that should be prescribed, which appears to be currently based on improvements to HbA1c. Eleven RCTs included in this systematic review [79, 80, 89-92, 94-96, 100-102] present HbA1c and insulin sensitivity data, with only one [79] indicating that insulin sensitivity did not improve when HbA1c improved. Furthermore, two studies [80, 90] indicated that insulin sensitivity improved but was not reflected in HbA1c, which did not change. Additionally, insulin sensitivity improved after 12 months of gym-based maintenance despite glycaemic control becoming worse [94]. Therefore, further investigations as to whether resistance training should be prescribed based on insulin sensitivity should be undertaken. If resistance training should be prescribed based on insulin sensitivity, it may need to be prescribed every day in this population, at least initially, as the length of time insulin sensitivity remains improved following a single resistance training session has not been adequately evaluated. After 12-16 weeks of training, improved insulin sensitivity appears to be maintained for four to five days [90, 91, 95], therefore glucose control may potentially be improved or maintained with one or two resistance training sessions each week. Both of these possibilities vary considerably from current recommendations of two-three days·wk^{-1} [50-52]. It is possible that resistance training should be performed more regularly initially to improve insulin sensitivity and glycaemic control, before it can be performed less frequently to maintain the benefits; however this is yet to be thoroughly examined.

The training environment and intensity of resistance training also need further investigation, as decreased compliance to the training protocol appears to be associated

with a decline in insulin sensitivity as demonstrated by the lower adherence level and increased insulin resistance reported with home-based training [89, 94]. While high adherence to resistance training protocols resulted in significant muscle strength improvements, changes in body mass were generally not observed. In contrast, lean body mass increased and percentage body fat decreased, confirming that body composition is improved with resistance training. Therefore resistance training may provide further benefits for individuals with diabetes attempting to lose weight as resistance training may counteract the loss of muscle mass typically associated with isolated hypocaloric diets [125]. However, changes to body composition are unlikely to account for any changes in insulin sensitivity, as this can be increased following a single exercise session [62, 63]. Although changes to body composition may not improve insulin sensitivity, individuals with diabetes are at an increased risk of cardiac co-morbidities for which improved body composition would reduce this risk. Additionally, resistance training has the ability to improve muscle quality (defined as a functional measure of strength per unit volume of muscle) and change the characteristics of a muscle fibre [91, 126], suggested to result in increased glucose transport. Although, limited data from individuals with diabetes suggest that muscle mass or body composition changes do not influence insulin sensitivity, local contraction-mediated responses from resistance training might [86], resulting in increased intracellular signalling [77] leading to increased membrane bound GLUT4 transporters and improved insulin sensitivity. Additional mechanisms of improved insulin sensitivity with exercise include increasing mithochondrial biogenesis, increased microvascular perfusion [127] along with modifying S-nitrosation levels [128]. Despite mechanisms for why resistance training improves insulin sensitivity not yet being fully elucidated, they are understood to have some common mechanisms to aerobic training as well as some unique adaptations attributable to resistance training alone [46,

113]. But improved insulin sensitivity from resistance training can be attributed to an increase in the amount of GLUT4 transporters that are available to promote glucose uptake and also by increasing insulin receptor stubtrate-1 associated PI-3K activity [129].

Although not reviewed in detail here, resistance training invokes many health benefits for individuals with diabetes in addition to improved glycaemic control. These include improvements in bone strength, minimisation of sarcopaenic losses or muscle weakness associated with aging, improved balance and reduced falls risk [130]. The beneficial effects of resistance training on lowering cardiovascular risk (ie. blood pressure and blood lipids) have been reviewed elsewhere [74]. Of the studies reviewed here, the impact of resistance training on lipid profiles is minimal in individuals who were normal or just above normal at baseline, but it is promising that positive blood pressure effects have been reported in hypertensive patients with T2D [81, 90, 92, 100, 114]. Decreasing body mass by dieting (energy restriction) has detrimental effects on muscle mass while aerobic training is only able to maintain the integrity of muscle [131] however, it is suggested that resistance training is able to counteract these detrimental effects in a way that aerobic training cannot by actually improving the amount and integrity of muscle mass [125].

2.6. Conclusion

Compelling evidence from both RCTs and non-RCTs is that resistance training is safe for individuals with diabetes who are likely to have complex co-morbidities, although it needs to be noted that all studies to date have excluded patients with contraindications to resistance training [132]. Of the 501 individuals who participated in resistance training interventions associated with a RCT, a total of 11 hypoglycaemic events were reported

with only one requiring medical attention, 26 individuals required their programs to be modified because of musculoskeletal injury and three individuals experienced episodes of chest pain. Resistance training is effective in improving glycaemic control and increasing insulin sensitivity. Higher intensity and longer intervention duration of resistance training appears most beneficial, but this along with training frequency, are parameters that require further investigation as some low intensity resistance training programs have reported metabolic benefits [101, 102, 107]. It is likely that individualised programs, taking into account an individual's current level of strength, severity of diabetes and also co-morbidities will optimise the adaptive response and enhance compliance. Determining the minimum effective dose of resistance training, or if appropriate in conjunction with aerobic training, would possibly improve ongoing compliance, and therefore lead to improved health outcomes. Resistance training has been shown to not only be equivalent to AT in ameliorating diabetes and its associated complications; it may also be the exercise of choice for individuals with diabetes or pre-diabetes who find adherence to continuous moderate intensity aerobic training too physically challenging.

Chapter 3

An investigation into the accuracy of cytometric bead assay for measuring adipose and inflammatory cytokines before and after exercise

3. An investigation into the accuracy of cytometric bead assay for measuring adipose and inflammatory cytokines before and after exercise

3.1. Preface

The initial challenge was to identify the most accurate method of performing blood analysis for the hormones and adipocytokines that were going to be measured throughout this series of studies. Enzyme-linked immunosorbent assay (ELISA) has traditionally been the most cost effective way to measure large volumes of most of these hormones and adipocytokines, however the recent advancement of technology through multiplex bead array assays (MBAA), theoretically improved both the time and cost efficiency of these measurements. The main advantage of using MBAA as opposed to traditional ELISA, is the ability to measure multiple adipocytokines and markers from the one small sample of serum or plasma. If the same accuracy can be gleaned from a smaller volume of blood with an increased volume of information, then a sound scientific, ethical and financial argument can be formed for MBAA being the most efficient and effective means of analysing adipoctyokine concentrations. Further, the ability to measure multiple outcomes from the single sample has long-term benefits in reducing overall costs of buying multiple ELISA kits and also significantly reducing human laboratory analysis time, thereby providing substantial financial savings. Therefore, it is important to compare the accuracy and agreement between these techniques.

3.2. Introduction

Pro- and anti-inflammatory cytokines have been implicated in health conditions such as obesity and type 2 diabetes [133] along with hypertension and cardiovascular disease

[134]. Methods of analysis such as the bead based cytokine assays and MBAA, where multiple cytokines can be measured with a very small amount of blood, are more frequently being used for the analysis of adipokines, cytokines and hormones. Concerns regarding sensitivity and accuracy of bead based cytokine assays have seemingly been allayed through findings of high precision and low variability when compared to World Health Organisation recognised standards [135]. However, whilst MBBA have also been found to correlate strongly with the commonly used enzyme-linked immunosorbent assay (ELISA), the accuracy and reliability of the absolute values obtained from MBBA and ELISA may differ and be dependent upon the vendor and the exact methods followed [136].

For example, Tarnok and colleagues [137] reported that the evaluation of interleukin-6 (IL-6), -8 (IL-8) and -10 (IL-10) by cytometric bead array (CBA) using a FACSCalibur flow cytometer and ELISA were very strongly correlated and identified similar very high concentrations in children who had undergone cardiovascular surgery. Likewise, positive correlations have been demonstrated between the data gained from CBA using a FACSCalibur flow cytometer and ELISA for tumour necrosis factor-alpha (TNF-α) and IL-6 in rodents with inflammatory lung disease [138]. However, while these results were positively correlated ($r = 0.66$ for TNF-α and $r = 0.92$ for IL-6), the TNF-α concentrations measured by CBA were approximately 1.8 fold higher than when measured by ELISA, indicating an issue with the accuracy of the method [138]. These discrepancies concur with findings by Jiménez et al. [139] who have highlighted poor accuracy of CBA, with plasma concentrations of IL-10 and TNF-α approximately 33% and 17% greater respectively, when derived by CBA using a FACSCalibur flow cytometer compared to ELISA in people with renal transplant rejection, despite the

values not being significantly different. The sensitivity of the CBA can be questioned from findings of higher concentrations of plasma IL-10 and TNF-α in patients with renal transplant rejection, while no concentration of TNF-α was reported in patients without renal transplant rejection [139].

As inflammatory cytokines such as IL-6, TNF-α and leptin appear to be affected by exercise [140, 141] and may be used as indicators of the acute and chronic adaptations to exercise, it is important to ascertain the validity and reproducibility of the CBA assay in the context of measurement of cytokines from blood, following exercise. Aspects of this have been undertaken by Timmons et al. [142] who investigated the effect of exercise in young healthy men and women on plasma IL-6 and TNF-α by CBA analysis performed using a FAC-Scan flow cytometer. Plasma IL-6 was detected in 73% of samples (63% pre-exercise and 84% post-exercise) and TNF-α was detected in 57% of samples by CBA, while ELISA detected IL-6 in 100% of plasma samples [142], indicating a potential problem with assay sensitivity. While there was strong statistical correlation between CBA and ELISA derived concentrations of IL-6, Bland-Altman plots revealed poor statistical agreement between the methods, with CBA derived concentrations typically being less than those derived through ELISA [142].

With this conflicting evidence in relation to the accuracy and sensitivity of CBA analysis using blood samples from a range of different health conditions and populations, the aim of this study was to investigate the sensitivity and reliability of CBA to measure cytokine concentrations in older individuals with and without type 2 diabetes (T2D). In this instance, we chose to compare three cytokines that are considered to play important roles in the pathophysiology of diabetes and typically are thought to respond to exercise [33]

using two analysis methods that are popular and regularly used and reported in the published literature. It was hypothesised that cytometric bead assay would be sensitive enough to accurately measure adipocytokines.

3.3. Methods

3.3.1. Subjects and study design

Ten individuals (six males, four females) with T2D treated with either diet alone or diet with oral hypoglycaemic medications and 10 apparently healthy individuals (three males, seven females) were recruited to undertake a single session of resistance exercise. Participants were interviewed by an accredited exercise physiologist to ensure they were inactive (not meeting the current exercise guidelines) and had not participated in resistance training for at least six months, and were screened according to criteria from the American College of Sports Medicine [143]. Physical activity levels were determined through extensive interviewing regarding their current exercise and incidental activity habits, asking questions specifically about how much walking, jogging, cycling or any other aerobic based leisure activities (such as golf or lawn bowls) they completed on a weekly basis. Participants were also questioned about their formal and informal resistance training habits (such as lifting heavy objects as part of their employment. Additionally, participants completed the short-form version of the International Physical Activity Questionnaire (IPAQ) [144].

Inclusion criteria for this study were: aged 40-69 years and were taking a stable dose of medications (if they were taking medications). Participants were excluded if they had: recent coronary event or established heart disease, uncontrolled hypertension (> 150/90

mmHg), neuropathy, orthopaedic disorder preventing them from completing resistance exercise, any medical condition that contraindicated resistance exercise, and being unable to understand English or follow instructions. Participants' mean ± SD age was 56.7 ± 8.2 years, with a mean ± SD height and body mass of 170.3 ± 7.7 cm and 80.7 ± 13.1 kg respectively. All participants provided written informed consent prior to any involvement and all aspects of the study were conducted in accordance with the Declaration of Helsinki and approved by the human research ethics committees of RMIT University and Austin Health.

Participants completed one-repetition maximum (1RM) testing on the five exercises to be included in the exercise session following a set protocol as reported previously [63], at least seven days before completing the resistance exercise intervention. Following a 12-hour overnight fast, participants travelled to the laboratory via a private vehicle where they had a fasting blood sample collected before consuming a standardised breakfast meal (toast and juice) and undertaking the resistance exercise session. The single session of progressive resistance exercise session consisted of three sets of 10 repetitions at loads consistent with 45%, 60% and 75% of their predetermined 1RM for five whole-body exercises (bench press, 45° leg press, shoulder press, 45˚ calf raises and lateral pull-down). Participants attended the laboratory again 24 hours after completing the resistance exercise session to provide another fasting blood sample. Participants recorded and replicated their evening meals prior to each visit and regular medications were withheld only during the fasting period and consumed after the fasting blood test.

Venous blood samples were collected using standard venepuncture techniques into a serum separating tube and allowed to clot on ice before being centrifuged at 5000g and

4°C for seven minutes, and the serum stored at -80°C for later analysis. Due to technical difficulties, the post exercise blood sample was unable to be collected from one individual with T2D and one apparently healthy individual was discovered to have extreme hyperinsulinaemia during baseline testing, resulting in these two individuals being excluded from the analysis. In total, 36 samples were analysed using both techniques.

3.3.2. Cytometric bead array analysis

Interleukin-6, TNF-α, leptin and resistin levels were determined by a commercially available FlowCytomix Assay (eBioscience, San Diego, USA) according to the manufacturer's instructions using 25µL of serum. According to the manufacturer's, the sensitivity of the respective assays were 1.2 $pg \cdot mL^{-1}$, 3.2 $pg \cdot mL^{-1}$, 0.05 $ng \cdot mL^{-1}$ and 1.7 $pg \cdot mL^{-1}$ for IL-6, TNF-α, leptin and resistin, respectively. After completing the test protocol, samples were transferred to FACS tubes and analysed by BD FACSCanto™ II flow cytometer (BD Biosciences, San Jose, CA, USA, RMIT Flow Cytometry Facility, RMIT Bundoora, Australia). Data recorded from the flow cytometer were then analysed using the eBioscience FlowCytomix Pro 2.4 Software (eBioscience, San Diego, USA). Concentrations of resistin were able to be determined through the CBA and therefore, this analyte was included in the CBA but not analysed by ELISA for comparative purposes. Samples were measured in duplicate to determine the coefficient of variation (CV). However, CV's could not be calculated for IL-6 and TNF-α due to the CBA assay failing to detect either of these cytokines in the samples. The CV's for leptin and resistin were 11.5% and 3.6% respectively.

Additionally, a 5-parameter curve was created from the intensity of known standards using GraphPad Prism 5.01 for Windows (GraphPad Software, La Jolla, CA, USA) with the concentrations of the unknown samples extrapolated from this to determine if there were any differences in concentration derived from the manufacturer's analysis software and an independent company's graphing computer software.

3.3.3. Enzyme-linked immunosorbent assay

Commercially available Quantikine ELISA kits were used to measure IL-6, TNF-α (R & D Systems, Minneapolis, MN, USA) and leptin (Millipore Corporation, Billerica, MA, USA) following the manufacturers protocol. According to the manufacturers, the sensitivity of the respective assays were 0.7 $pg \cdot mL^{-1}$, 1.6 $pg \cdot mL^{-1}$ and 0.5 $ng \cdot mL^{-1}$ for IL-6, TNF-α and leptin respectively. A 5-parameter curve was created from the known standards using GraphPad Prism 5.01 for Windows with the concentrations from the unknown samples extrapolated. Samples were measured in duplicate and the CV of each assay was 3.2%, 2.7% and 2.8% for IL-6, TNF-α and leptin, respectively.

3.3.4. Statistical analysis

All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of $p = 0.05$. Leptin concentrations derived through both ELISA and CBA were not normally distributed and therefore underwent log transformation before being subjected to statistical analysis. No concentrations of IL-6 or TNF-α were detected by CBA, meaning that no comparative analyses were able to be undertaken for these cytokines, therefore all further statistical analyses relate only to leptin concentrations. Two-way repeated measures ANOVA (diabetes status x time)

indicated there was no difference in the response to exercise for those with and without T2D using either CBA or ELISA ($p > 0.05$; data not shown), therefore the two populations were treated as one group for the remaining analyses. A mixed between-within repeated measures ANOVA (assay x time) was then completed to assess the variation between CBA and ELISA. A Pearson correlation was used to assess the statistical correlation between CBA and ELISA derived results. A two-way ANOVA (CBA vs ELISA) with a Tukey post-hoc analysis was then undertaken to assess whether the two assays produced the same or different values. Statistical agreement between CBA and ELISA was assessed using a Bland-Altman plot performed with GraphPad Prism 5.01 for Windows. Finally, a paired T-test (two-tailed) was conducted to assess the differences in leptin concentration generated using the manufacturers software (eBioscience) and the independent company's graphing software (GraphPad). Data are presented as mean ± SD or 95% confidence intervals (CI), as specified.

3.4. Results

Concentrations of IL-6 and TNF-α were detected in 94% and 47% of samples respectively by ELISA however, the CBA failed to detect IL-6 or TNF-α in any of the samples. Both ELISA and CBA assays detected leptin in 100% of the samples; however the two assay methods produced significantly different values ($p < 0.001$; Table 3.1). There was no statistically significant change following exercise compared to the pre exercise value for any cytokine with either assay method ($p > 0.05$).

Table 3.1: **Comparison of cytokine concentrations as determined by CBA and ELISA assays**

	CBA	ELISA
IL-6 (pg·mL^{-1}; N=18)		
All Samples	0 ± 0.0	5.5 ± 2.5*
TNF-α (pg·mL^{-1}; N=18)		
All Samples	0 ± 0.0	1.4 ± 1.6*
Leptin (ng·mL^{-1}; N=18)$^{\#}$		
All Samples	46.8 ± 33.0	21.8 ± 18.0*

All samples are participants both with and without diabetes as there was no significant difference between populations. Data are mean ± SD with analysis conducted using two-way ANOVA. *Significant difference when compared to CBA determined concentration ($p < 0.001$). $^{\#}$Leptin concentrations were log transformed prior to statistical analysis and have been reported as actual concentrations. CBA = cytometric bead array; ELISA = Enzyme-linked immunosorbent assay; IL-6 = Interleukin-6; TNF-α = Tumour necrosis factor-alpha

There was no significant assay x time interaction ($p = 0.96$) and the significant difference ($p < 0.001$) in the concentrations of leptin found between assays, both prior to and following exercise are illustrated in Figure 3.1, with the CBA producing higher values than the ELISA. There was a strong statistical correlation between the CBA and ELISA derived leptin concentration (Pearson's $r = 0.93$, $p < 0.001$; Figure 3.2). Overall, the statistical agreement between the assays for determining leptin concentrations was poor, with the CBA assay overestimating the ELISA determined values by an average of 25.05 ng·mL^{-1} (115%; Figure 3.3). There was also a significant degree of heteroscedasity present as indicated by the significant negative correlation between the average values from both assays and the difference in the values between assays ($r = -0.79$, $p < 0.001$; Figure 3.3). There was no difference in CBA determined concentrations of leptin when analysed by the manufacturer's software or when generated from the 5-parameter standard curve ($p = 0.85$).

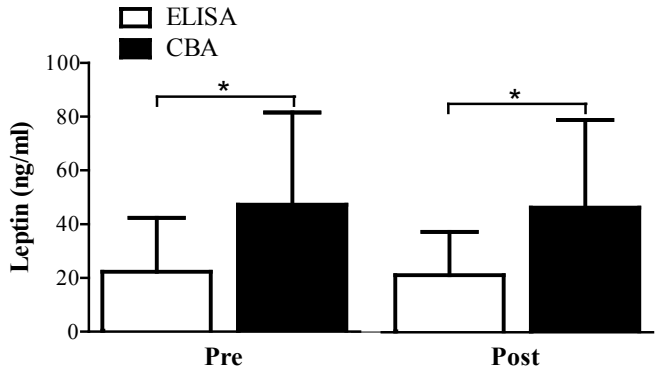

Figure 3.1: **Comparison of methods for measuring leptin concentration.**
Leptin concentrations measured by ELISA (open bars) and CBA (solid bars) assays in older sedentary humans with and without type 2 diabetes prior to and 24 hours following resistance exercise (RE). Values are mean ± SD. *Significant difference between assays, $p < 0.001$

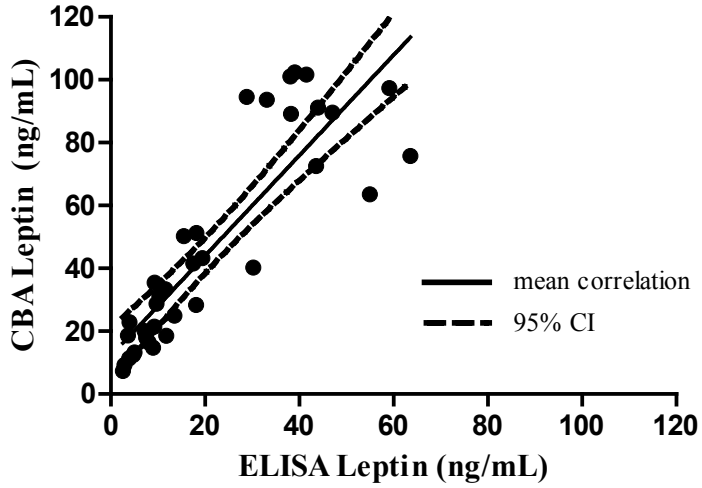

Figure 3.2: **Pearson correlation of leptin concentrations measured by ELISA and CBA assays.**
Thirty-six pairs of data available for comparison.

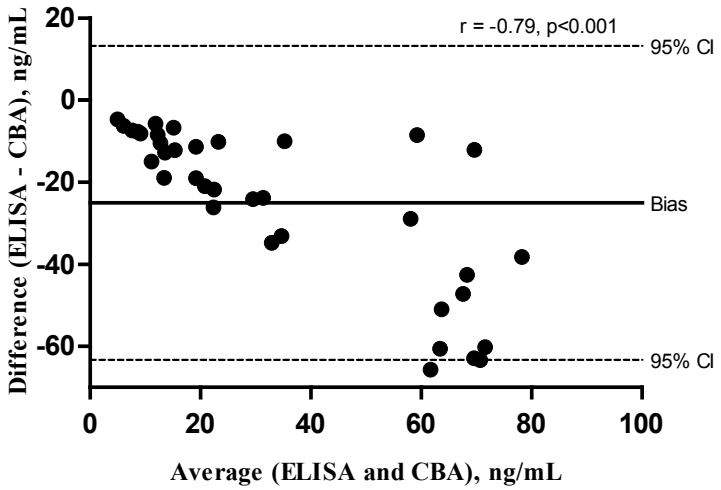

Figure 3.3: **Bland-Altman limits of agreement of leptin concentrations measured by ELISA and CBA assays.**
Bias = -25.05 ng·mL^{-1} (95% CI: -63.28 to 13.18). Thirty-six pairs of data available for comparison.

3.5. Discussion

This study compared the ability of a commercially available CBA assay with a commercially available ELISA assay to determine concentrations of IL-6, TNF-α and leptin in older individuals with and without T2D within a single laboratory. With the increasing amount of research being conducted on adipose derived cytokine markers of inflammation, particularly in conditions of obesity and T2D, it is important to confirm the accuracy and reliability of an increasingly popular method that allows simultaneous detection of multiple cytokines in a single, small sample of serum against another commonly used method that analyses only a single cytokine. We chose to compare the statistical relationship and agreement for IL-6, TNF-α and leptin that have been shown to be implicated in obesity and T2D and also respond to exercise.

Although there was good reliability of the CBA for leptin with an intra-assay CV of 11.5%, concentrations of IL-6 or TNF-α were not detected. This is despite IL-6 being detected in 94% of samples and TNF-α being detected in 47% of samples with ELISA

assays. This suggests that when following the manufacturer's specifications, the CBA is not sensitive enough to measure IL-6 or TNF-α in these older individuals either with or without type 2 diabetes. Importantly, this does not seem to be a problem with the curve fitting software, as two different software packages resulted in the same concentration of leptin calculated from the CBA data.

While leptin was detected in all samples using both CBA and ELISA assays, the statistical agreement between the assays was poor; despite a strong correlation. This concurs with results reported by Timmons and colleagues [142] in young healthy individuals, and along with data from Young and colleagues [138], continues to suggest that CBA derived concentrations of cytokines over-estimate the actual concentration when compared to the commonly used method of ELISA.

While IL-6 or TNF-α was not detected by CBA in this study, others have also reported difficulties detecting these cytokines, with concentrations detected in 73% and 48% of samples, respectively by CBA [142]. The findings from this study in a population of older adults with and without a chronic medical condition are in contrast to results reported by Jiménez and colleagues [139] who found that IL-5 was detected by CBA but not by ELISA. This particular study though was conducted in patients who had undergone kidney transplantation with some suffering from renal rejection. These contrasting findings highlight the inflammatory nature of acute medical conditions along with the reduced sensitivity of the CBA assay when trying to determine concentrations of multiple cytokines from the one sample. Therefore, despite the attractiveness of the CBA from both a time and cost perspective to measure multiple cytokines, unless participants are acutely unwell, it is unlikely that CBA derived concentrations will be able to fully

reflect the level of these cytokines. This may be due to a sensitivity issue with the beads being unable to 'capture' the desired cytokine, although equally it may be due to the ability of the multiplexing device to detect the captured cytokine on the beads. Where general flow cytometry (such as the CBA) use a combination of different size microsphere's and colour intensities to identify individual cytokines, Luminex technology uses a single size microsphere and a proprietary dying process to identify individual cytokines. However, while the Luminex technology may provide slightly more accurate values than CBA through advancing the techniques used for flow cytometry, issues still remain [145].

The lack of response of these cytokines to a session of resistance exercise is somewhat surprising given that others have reported exercise derived changes [33, 146], however there is evidence to suggest that the response to acute resistance exercise is variable [147]. The CBA and ELISA are two of the most common techniques reported for determining hormone and cytokine concentration in the published literature and based on our data, although the CBA may have an application in some circumstances, caution needs to be used when comparing data generated through CBA for numerous cytokines measured from a small sample of human blood compared to data generated for a single cytokine using ELISA.

3.6. Conclusion

When following the manufacturer's instructions, the CBA assay conducted in our laboratory is not sensitive enough to detect all of the desired cytokines, as the CBA assay was unable to detect IL-6 or TNF-α despite these cytokines being detected by ELISA. It can also be concluded that when the CBA assay does detect cytokines, its accuracy is

questionable as it was found that leptin was over-estimated by 115% when compared to ELISA, thereby rejecting the hypothesis. While this investigation found the accuracy and sensitivity of the low-cost, time effective CBA assay to be questionable, further research and development is justified because of its strong correlation with ELISA for leptin. Further research using laboratory validated standards is also justified to confirm these results. Additionally, further research could investigate whether modifying the manufacturer assay protocol, specifically determining whether the volume of sample used can modulate results. Until these results are confirmed, based on these data, it is advisable that caution is used when comparing cytokine concentrations derived through CBA and ELISA methods and that researchers conduct their own internal testing to determine the most accurate methods for their laboratories.

Chapter 4

An investigation of the reproducibility of multiple repeated oral glucose tolerance tests

4. An investigation of the reproducibility of multiple repeated oral glucose tolerance tests

4.1. Preface

Following the determination that blood samples analysed through cytometric bead array do not detect the same concentration of hormones and adipocytokines as an ELISA (Chapter 3), analysis was conducted using ELISA. The next requirement was to determine whether oral glucose tolerance tests completed on consecutive days provided a consistent estimate of insulin sensitivity to see if it is an appropriate method to use to measure change following exercise in people with type 2 diabetes. This chapter is based on a peer-reviewed paper published in Diabetes Research and Clinical Practice [148] (Appendix A).

4.2. Introduction

Insulin sensitivity is regularly estimated through the use of an oral glucose tolerance test (OGTT) with a number of equations showing good correlation with the gold standard method, the euglycaemic-hyperinsulinaemic clamp [149]. However, issues concerning glucose load (50 g to 100 g), reproducibility and diurnal variation of the OGTT have been reported [24], with reliability questioned [150, 151]. Reproducibility investigations have centred on variables around the testing conditions, including glucose load [58], time of day [59], and the fasting period prior to testing [57, 59]. And while many studies have reported variations in glucose response from multiple or repeated OGTTs [48, 59, 150, 151], none have looked at the reproducibility of OGTTs repeated on consecutive days. So in light of this, it was important to analyse the glucose and insulin responses in apparently healthy individuals to determine whether OGTTs are reliable to estimate

insulin sensitivity on consecutive days. Therefore, the aim of this study was to investigate whether insulin sensitivity was affected by repeated daily OGTTs and it was hypothesised that oral glucose tolerance tests repeated on four consecutive days would produce similar estimates of insulin sensitivity.

4.3. Methods

4.3.1. Participants and study design

Ten inactive, apparently healthy individuals with no diagnosed metabolic conditions took part in this trial. Inclusion criteria were: aged 40-69 years, taking no medications influencing metabolism, and not having participated in resistance training in the last six months or completing regular aerobic exercise. Exclusion criteria included: recent coronary event or established heart disease, uncontrolled hypertension (> 150/90 mmHg), neuropathy and being unable to understand English or follow instructions. They completed the self-report International Physical Activity Questionnaire [144] and were instructed not to complete any structured or specific exercise during the study, record all food consumed in a food diary and replicate their diet before each OGTT. Participant characteristics are presented in Table 4.1.

The study protocol is presented schematically in Figure 4.1 and was approved by the RMIT University Human Research Ethics Committee with written informed consent obtained prior to participation. Participants arrived at the research facility between 0600 and 0900 by private vehicle, following a 12-hour overnight fast. Anthropometric measurements and a fasting blood sample were collected before participants undertook an OGTT to obtain baseline glucose and insulin responses [10]. Participants then

returned to the research facility to undergo further OGTTs on the three subsequent mornings.

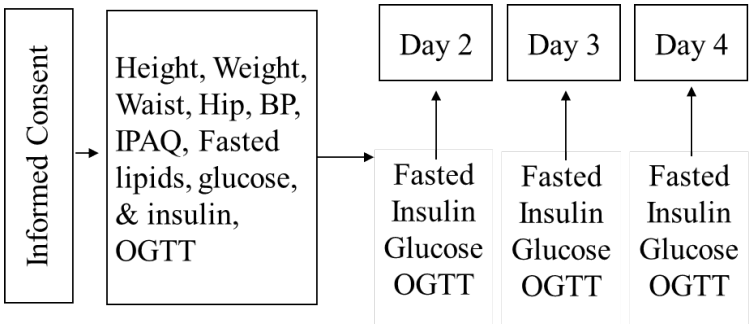

Figure 4.1: Study protocol
Waist = waist circumference; Hip = hip circumference; BP = blood pressure; Lipids = cholesterol profile; IPAQ = international physical activity questionnaire; OGTT = oral glucose tolerance test

4.3.2. Blood sampling and analysis

A cannula was inserted into an antecubital vein with blood samples obtained before consuming 75 g of glucose in 300 ml of water (Gluco Scan, BIOCORP Aust Pty. Ltd.). Further blood samples were collected at 30, 60, 90 and 120 minutes after consuming the glucose, with patency maintained by flushing with saline, and the first 2 ml of blood collected being discarded.

Lipid profiles and glycaemic control (HbA1c) were measured in a commercial laboratory. Glucose and insulin were measured using the YSI 2300 Stat Plus analyser (Yellow Springs, USA) and Millipore human insulin ELISA kits respectively. Area under the curve (AUC) was calculated by a computer-based trapezoidal model and insulin sensitivity estimated by the oral glucose insulin sensitivity (OGIS) index [152] and the Stumvoll insulin sensitivity index [153].

Table 4.1: **Participant demographics**

Outcome Measure (units)	Mean ± SD
Male / Female	3 / 7
Age (years)	54.6 ± 6.5
Body mass (kg)	93.4 ± 16.4
Height (cm)	167.7 ± 6.8
BMI ($kg \cdot m^{-2}$)	33.3 ± 6.3
Waist Circumference (cm)	98.8 ± 12.6
Waist:Hip	0.88 ± 0.08
SBP (mmHg)	126 ± 14
DBP (mmHg)	83 ± 10
Cholesterol ($mmol \cdot L^{-1}$)	4.9 ± 1.2
LDL-C ($mmol \cdot L^{-1}$)	2.8 ± 1.0
HDL-C ($mmol \cdot L^{-1}$)	1.42 ± 0.24
Triglycerides ($mmol \cdot L^{-1}$)	1.6 ± 0.5
HbA1c (%)	5.5 ± 0.3
Glucose ($mmol \cdot L^{-1}$)	5.3 ± 0.3
Insulin ($pmol \cdot L^{-1}$)	130.1 ± 82.1
Activity ($MET\text{-}min \cdot wk^{-1}$)	1428 ± 1365
Sedentary Time (min)	435 ± 207

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; HbA1c = glycated haemoglobin; MET = metabolic equivalents

4.3.3. Statistical analysis

All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of $p = 0.05$ and a Bonferroni correction made for multiple analyses. A repeated measures analysis of variance (ANOVA) was completed to determine change over time of the overall outcomes and to determine the reliability of the change scores from each independent time-point for each repeated measure. Change was calculated by subtracting the follow-up score from the initial score and to provide an

indication of repeatability, coefficient of variation was calculated for each individual by dividing the standard deviation of their results from their four tests by their mean result. Data are presented as means (95% confidence intervals (CI)) unless otherwise indicated. Approximately 4% of glucose and insulin data points were missing (due to occlusions within the cannula) and were substituted by bringing the last known value for that time point forward to ensure AUC was calculated from five time-points [154].

4.4. Results

We failed to detect any statistically significant change in glucose or insulin response or insulin sensitivity over the 4-days of repeated, daily OGTTs (Table 4.2; $p = 0.20$). There were also no significant differences in the change scores for glucose AUC ($p = 0.37$), insulin AUC ($p = 0.22$), OGIS ($p = 0.41$) or Stumvoll ISI ($p = 0.12$; Table 4.3).

At baseline, two participants were considered to have extreme hyperinsulinaemia (insulin ≥ 200 pmol·L^{-1}). One individual with extreme hyperinsulinaemia was classified as having impaired glucose tolerance (2-hour glucose ≥ 7.8 mmol·L^{-1}) using the World Health Organisation criteria [10] at baseline, 24-hour and 48-hour testing, before reverting to a classification of normal glucose tolerance at the final test. At baseline, all other individuals were considered to have normal glucose tolerance however, impaired glucose tolerance classifications were present for one individual at the second OGTT (2-hour glucose = 8.7 mmol·L^{-1}) and a different individual at the final OGTT (2-hour glucose = 8.0 mmol·L^{-1}).

The glucose, insulin and insulin sensitivity responses are presented in Figure 4.2 and clearly show that as a group, the response is similar from test to test. However, the

individuals with hyperinsulinaemia clearly responded differently and have marked variation in their response. When only those with normal fasting insulin levels at baseline were considered (N = 8), the change scores were generally smaller and were still similar for glucose AUC (p = 0.17), insulin AUC (p = 0.41), OGIS (p = 0.15) and the Stumvoll ISI (p = 0.34). Effect sizes (partial eta squared) of these changes were large [56], with values of 0.608, 0.410, 0.625 and 0.461 respectively. Excluding the individuals with extreme hyperinsulinaemia, the mean (range) coefficient of variation for individuals from day to day was 6.3% (1.1% - 13.4%), 20.6% (6.8% - 48.0%), 7.8% (4.2% - 14.2%) and 14.4% (0.3% - 43.3%) for glucose AUC, insulin AUC, OGIS and Stumvoll ISI respectively.

The clinically relevant change (calculated by the change from the first test to the second ± the 95% CI) in the response to an OGTT in apparently healthy individuals for glucose and insulin response along with insulin sensitivity is presented in Table 4.3. From a practical perspective, if these confidence intervals were converted into unit values, they would infer that glucose AUC increases of greater than 63.5 $mmol \cdot L^{-1} \cdot 120min^{-1}$ and decreases of greater than 80.9 $mmol \cdot L^{-1} \cdot 120min^{-1}$ exceed the combined daily measurement and biological variation and can therefore be viewed with confidence as indicating real unfavourable and favourable changes respectively. The same can be applied to insulin AUC increases of greater than 7,061 $pmol \cdot L^{-1} \cdot 120min^{-1}$ and decreases of greater than 7,237 $pmol \cdot L^{-1} \cdot 120min^{-1}$ indicating real unfavourable and favourable changes respectively with real unfavourable and favourable changes for OGIS respectively being a decrease of greater than 1.2 $ml \cdot min^{-1} \cdot m^{-2}$ and an increase of greater than 52.7 $ml \cdot min^{-1} \cdot m^{-2}$. The real unfavourable and favourable changes for Stumvoll ISI

are a decrease of greater than 0.008 index units and an increase of greater than 0.010 index units respectively.

Table 4.2: **Glucose, insulin and insulin sensitivity response to consecutive OGTTs. Mean (95% confidence interval).**

Outcome	Baseline (0 hours)	24 hours	48 hours	72 hours
N = 10				
2-hr Glucose ($mmol \cdot L^{-1}$)	6.2 (5.1 – 7.3)	5.8 (4.4 – 7.2)	5.9 (4.7 – 7.1)	5.9 (4.8 – 7.1)
Glucose AUC ($mmol \cdot L^{-1} \cdot 120min^{-1}$)	855.7 (741.3 – 970.2)	839.6 (690.1 – 988.6)	882.7 (706.3 – 1059.1)	866.2 (674.6 – 1057.7)
2-hr Insulin ($pmol.L^{-1}$)	743.1 (214.0 – 1272.2)	676.1 (150.7 – 1201.5)	729.5 (213.2 – 1245.9)	595.6 (184.1 – 1007.1)
Insulin AUC ($pmol \cdot L^{-1} \cdot 120min^{-1}$)	91851 (43944 – 139759)	142206 (18470 – 265941)	122431 (40811 – 204051)	104306 (54934 - 153677)
OGIS ($ml \cdot min^{-1} \cdot m^{-2}$)	333.6 (282.2 – 385.0)	351.8 (275.2 – 428.4)	373.0 (309.7 – 436.3)	372.9 (299.7 – 446.1)
Stumvoll ISI (arbitrary units)	0.047 (0.003 – 0.091)	0.051 (0.007 – 0.095)	0.046 (0.002 – 0.089)	0.056 (0.020 – 0.092)
N = 8				
2-hr Glucose ($mmol \cdot L^{-1}$)	5.8 (4.9 – 6.7)	5.8 (4.3 – 7.3)	5.8 (4.7 – 6.8)	5.9 (4.6 – 7.3)
Glucose AUC ($mmol \cdot L^{-1} \cdot 120min^{-1}$)	835.0 (720.3 – 949.8)	826.3 (675.5 – 977.1)	873.7 (703.5 – 1043.9)	870.0 (653.8 – 1086.2)
2-hr Insulin ($pmol \cdot L^{-1}$)	531.7 (71.4 – 992.0)	516.4 (96.1 – 936.7)	586.2 (119.4 – 1052.9)	486.6 (134.7 – 838.5)
Insulin AUC ($pmol \cdot L^{-1} \cdot 120min^{-1}$)	62672 (40630 – 84714)	62584 (38235 -86933)	77443 (40909 – 113976)	85505 (34296 – 136713)
OGIS ($ml \cdot min^{-1} \cdot m^{-2}$)	354.0 (301.3 – 406.7)	379.8 (318.8 – 440.7)	363.8 (282.1 – 445.4)	377.5 (300.9 – 454.1)
Stumvoll ISI (arbitrary units)	0.067 (0.028 – 0.106)	0.068 (0.027 – 0.108)	0.061 (0.018 – 0.104)	0.069 (0.035 – 0.104)

AUC = area under the curve, OGIS = oral glucose insulin sensitivity index, ISI = insulin sensitivity index.

Table 4.3: **The observed change (variation) for each repeated measure for glucose and insulin AUC, OGIS and Stumvoll ISI. Mean (95% CI).**

Outcome	Change 1	Change 2	Change 3	Change 4	Change 5	Change 6
N = 10						
Glucose AUC ($mmol \cdot L^{-1} \cdot 120min^{-1}$)	-16.1 (-77.6 – 45.4)	27.0 (-56.5 – 110.4)	10.4 (-94.2 – 115.0)	43.1 (-1.4 – 87.5)	26.5 (-57.3 – 110.4)	-16.6 (-75.1 – 42.0)
Insulin AUC ($pmol \cdot L^{-1} \cdot 120min^{-1}$)	50354.3 (-32581.7 – 133290.3)	30579.4 (-7999.9 – 69158.7)	12454.3 (-18172.3 – 43080.9)	-19774.9 (-99968.1 – 60418.3)	-37900.0 (-139828.4 – 64028.4)	-18125.1 (-70054.3 – 33804.1)
OGIS ($ml \cdot min^{-1} \cdot m^{-2}$)	18.2 (-22.8 – 59.2)	39.4 (-16.4 – 95.2)	39.3 (-7.7 – 86.3)	21.2 (-51.2 – 93.6)	21.1 (-19.4 – 61.6)	-0.1 (-52.1 – 51.9)
Stumvoll ISI (arbitrary units)	0.004 (-0.008 – 0.016)	-0.001 (-0.013 – 0.011)	0.009 (-0.004 – 0.022)	-0.006 (-0.012 – 0.001)	0.005 (-0.006 – 0.016)	0.010 (0.001 – 0.020)
N = 8						
Glucose AUC ($mmol \cdot L^{-1} \cdot 120min^{-1}$)	-8.7 (-80.9 – 63.5)	38.7 (-44.4 – 121.7)	35.0 (-87.3 – 157.3)	47.4 (0.4 – 94.4)	43.7 (-61.7 – 149.1)	-3.7 (-72.0 – 64.7)
Insulin AUC ($pmol \cdot L^{-1} \cdot 120min^{-1}$)	-88.1 (-7237.1 – 7060.9)	14770.6 (-3586.9 – 33128.1)	22832.9 (-11855.2 – 57520.9)	14858.8 (-1571.5 – 31289.0)	22921.0 (-12737.0 – 58579.0)	8062.3 (-23063.2 – 39187.7)
OGIS ($ml \cdot min^{-1} \cdot m^{-2}$)	25.7 (-1.2 – 52.7)	9.8 (-33.5 – 53.0)	23.5 (-6.6 – 53.6)	-16.0 (-43.6 – 11.6)	-2.3 (-28.7 – 24.2)	13.8 (-19.1 – 46.6)
Stumvoll ISI (arbitrary units)	0.001 (-0.008 – 0.010)	-0.006 (-0.016 – 0.004)	0.002 (-0.007 – 0.011)	-0.007 (-0.014 – 0.001)	0.001 (-0.009 – 0.012)	0.008 (-0.002 – 0.019)

AUC = area under the curve, OGIS = oral glucose insulin sensitivity index, ISI = insulin sensitivity index, Change 1 = 24 hours minus baseline, Change 2 = 48 hours minus baseline, Change 3 = 72 hours minus baseline, Change 4 = 48 hours minus 24 hours, Change 5 = 72 hours minus 24 hours, Change 6 = 72 hours minus 48 hours

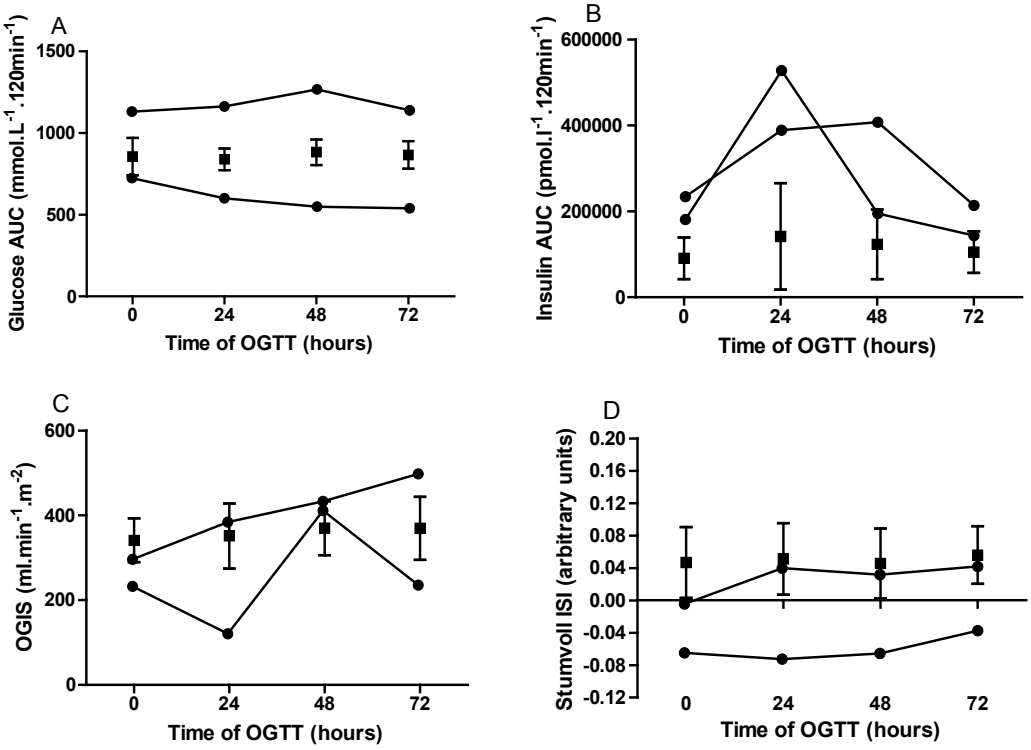

Figure 4.2: Glucose, insulin & insulin sensitivity response over four consecutive days.
Mean (■) and 95% CI for Glucose AUC (A), Insulin AUC (B), OGIS (C) and Stumvoll ISI (D) with individual responses of participants (N = 2) with extreme hyperinsulinaemia plotted (●) to show the variation.

4.5. Discussion

The OGTT has previously been reported to have unsatisfactory reproducibility in apparently healthy individuals [151] and those with mild diabetes [150] when the tests were repeated within two and seven days. This study has shown that the glucose and insulin response in apparently healthy individuals without hyperinsulinaemia is quite consistent and produced reliable results for insulin sensitivity (OGIS CV = 7.8%, Stumvoll ISI CV = 14.4%) from consecutive, repeated OGTTs. However, in those individuals who exhibited hyperinsulinaemia, in order to maintain glucose homeostasis, the findings suggest that repeated OGTTs may not produce a reliable estimation of insulin sensitivity.

However, it is difficult to interpret why these results do not concur with those published previously who have undertaken repeated OGTTs between two and seven days apart [150, 151], as participant demographic data were not reported. In the study by Olefsky and Reaven [151], it is reported that the average response to the two tests are quite similar, but there appears to be large amounts of intra-individual variability with glucose response at two hours varying by greater than 10% in 17 out of 31 cases and 12 of these 17 varied by greater than 20%. Similarly for insulin response at two hours, 21 out of 31 cases varied by greater than 20% with 11 of these 21 cases varying by more than 50% [151]. This is compared to the range of variation observed in this study for glucose response of between 1% and 13% in the eight participants who were not hyperinsulinaemic.

The data on the variation in glucose and insulin sensitivity response is an important finding and is something that has not been reported previously, especially given that numerous studies (including randomised controlled trials) involving resistance training in individuals' with type 2 diabetes that have used the OGTT to estimate insulin sensitivity [62, 63, 80, 90, 113]. One of the randomised controlled trials that used the OGTT to measure glucose change after an eight week intervention, was the initial resistance training randomised controlled trial [80] which was heavily relied upon for the formation for the initial resistance training guidelines for individuals with type 2 diabetes [55]. While this suggests that the findings from these trials that have used the OGTT in people with type 2 diabetes need to be cautiously interpreted, the limitations of this study also need to be considered. Although the large effect sizes and small 95% confidence interval range supports the clinical relevance of these findings for glucose, insulin and insulin sensitivity response, the small sample size, and particularly small for individuals with

hyperinsulinaemia, may limit the ability for this finding to be generalised to the diabetic population.

4.6. Conclusion

Through this small study of apparently healthy individuals without hyperinsulinaemia it can be suggested that the OGTT appears to be an appropriate method to estimate and measure change in insulin sensitivity over time, proving the hypothesis to be correct. However, other methods might be more appropriate for individuals with impaired glucose metabolism such as individuals with pre-diabetes or T2D.

Chapter 5

An investigation into the insulin sensitivity response to a single resistance exercise session in apparently healthy individuals

5. An investigation into the insulin sensitivity response to a single resistance exercise session in apparently healthy individuals

5.1. Preface

Following the conclusion that oral glucose tolerance tests were reliable to measure change in insulin sensitivity in apparently healthy individuals with good glucose homeostasis (Chapter 4), the oral glucose tolerance test was employed to determine the effect of a single session of resistance exercise on insulin sensitivity in apparently healthy individuals. This chapter is based on a peer-reviewed paper accepted for publication in Journal of Endocrinological Investigation [155] (Appendix A).

5.2. Introduction

Insulin resistance is a condition where the tissues (specifically skeletal muscle and the liver) are less responsive or sensitive to insulin, resulting in decreased glucose uptake. This results in increased insulin secretion and abnormally high levels of circulating insulin (hyperinsulinaemia) in an attempt to maintain glucose homeostasis [29]. Low grade inflammation has been associated with conditions of insulin resistance and obesity [35], while both conditions are independent risk factors for the development of hypertension and type 2 diabetes (T2D) [9, 36, 156]. This condition is distinct from overt T2D, where the pancreas is unable to adequately increase insulin secretion to account for the decreased insulin action [29].

Chronic exercise training, in the form of moderate-intensity aerobic type activities, has been shown to reduce fasting glucose levels, improve glycated haemoglobin levels (HbA1c) and increase insulin sensitivity [75]. More recently, resistance training has been

identified as a modality that is also capable of improving glucose levels and insulin sensitivity, as well as being associated with other health benefits such as improved body composition, blood pressure, lipid profiles and bone strength [132]. In relation to metabolic health, it is accepted that higher intensity resistance training is of greater benefit than lower intensity training, however the required frequency to maintain or continue these improvements remains unclear [70].

In the context of insulin sensitivity and glucose homeostasis, there have been few studies that have investigated the acute effects of resistance exercise in healthy individuals [65, 66, 68] and/or those with T2D [62, 63]. In those studies that have been published, the results are equivocal, with increased insulin sensitivity 24 hours after a single session of resistance exercise [64], and increased insulin action approximately 36 hours after unaccustomed eccentric resistance exercise [67]. However, Howlett and colleagues [66] refute these findings, suggesting that a single bout of resistance exercise impairs insulin action.

Furthermore, the ongoing effects of a single bout of resistance exercise are unknown, with no studies tracking the insulin or glucose response beyond 36 hours following the exercise bout. Without such knowledge it is difficult to determine the optimal rest interval between acute bouts of resistance exercise and hence, the optimal training frequency. This is an important consideration for middle-aged adults who are more commonly at risk of developing diabetes and often have the perception of having decreased time available to exercise between work and family commitments [157].

It was therefore the aim of this study to investigate the insulin sensitivity response using oral glucose tolerance tests administered on each of the four days following a single bout of moderate-high intensity resistance exercise, to determine the period of time that any changes were present. It was also hypothesised that a single session of resistance exercise would not modulate insulin sensitivity in apparently healthy individuals

5.3. Methods

5.3.1. Participants and study design

Ten inactive (completing less than 20 minutes of aerobic exercise twice weekly), apparently healthy males (N = 3) and females (N = 7) with a mean ± SD age of 51.6 ± 5.8 years with no diagnosed metabolic conditions were enrolled to participate. Ethical approval was granted from the RMIT University and Austin Health Human Research Ethics Committees, and all participants provided written informed consent. This study conformed to the principles of the Declaration of Helsinki. Inclusion criteria were: aged 40-69 years, taking no medications influencing metabolism, and not having participated in resistance training in the last six months. Exclusion criteria included: recent coronary event or established heart disease, uncontrolled hypertension (> 150/90 mmHg), neuropathy, orthopaedic disorder preventing them from completing resistance training, any medical condition that contraindicated resistance training, and being unable to understand English or follow instructions.

All participants arrived at the research facility between 0600 and 0900 hours by the use of private vehicles, following a 12-hour overnight fast and had height (QuickMedical stadiometer to the nearest 0.1 cm), body mass (Tanita, BWB-600, to the nearest 0.1 kg),

waist and hip circumference (using a standard non-elastic tape, to the nearest 0.1 cm) measured following recognised procedures [143]. They also had a fasting blood sample collected before undergoing an oral glucose tolerance test (OGTT) according to World Health Organisation protocols to obtain baseline glucose and insulin responses [10]. The OGTT was conducted by inserting a cannula into an antecubital vein with blood samples obtained before consuming 75 g of glucose mixed in 300 ml of water (Gluco Scan, BIOCORP Aust Pty. Ltd.). Further blood samples were collected at 30, 60, 90 and 120 minutes after consuming the glucose, with patency maintained by flushing with saline every 15 minutes. The first 2 ml of blood collected was discarded to ensure there was no saline in the sample. The study protocol is presented schematically in Figure 5.1.

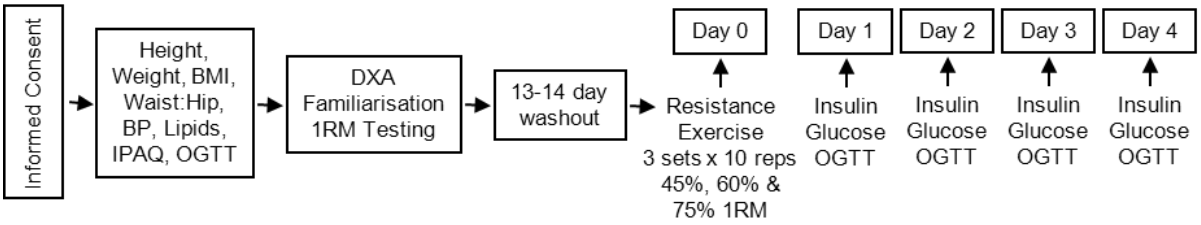

Figure 5.1: Study protocol
BMI = body mass index; Waist:Hip = waist to hip circumference ratio; BP = blood pressure; Lipids = cholesterol profile; IPAQ = international physical activity questionnaire; OGTT = oral glucose tolerance test; DXA = dual x-ray absorptiometry; 1RM = one repetition maximum; reps = repetitions

Participants returned to the research facility three to four days after their initial OGTT and underwent dual x-ray absorptiometry (DXA) before being familiarised with the resistance exercise equipment. Participants then underwent one repetition maximum (1RM) testing on all five exercises to be included in the resistance exercise bout. One repetition maximum testing followed a set protocol as reported previously [63]. Following a 13-14 day wash-out period, participants returned to the research facility to undergo the resistance exercise bout consisting of three sets of 10 repetitions for five whole-body exercises (bench press, 45˚ leg press, shoulder press, 45˚ calf raises and

lateral pull-down) at 45%, 60% and 75% of 1RM. The resistance training protocol was based on protocols used in similar previous research [63, 65]. Participants returned to the research facility after a 12-hour overnight fast to complete an OGTT for each of the next four days following the exercise session.

Participants completed the self-report International Physical Activity Questionnaire [144] prior to beginning the study to assess activity levels. Participants were asked to record all food consumed throughout the study period in a food diary (with an example provided) and were instructed to replicate their diet before each OGTT. Nutritional analysis was conducted by the same researcher on the FoodWorks 2007 (Xyris software (Australia) Pty Ltd., xyris.com.au) dietary analysis computer program version 5, service pack 1, to compare total energy consumed and the volume (grams) of protein, fat and carbohydrate each day.

5.3.2. Blood sampling and analysis

Baseline fasting blood samples were collected in serum separator tubes and an EDTA containing tube. These were sent to a commercial laboratory for analysis of lipid profiles (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides with coefficients of variation (CVs) of 2%, 9%, 12% & 3.5% respectively) and glycated haemoglobin (HbA1c: CV = 3%). Additional samples were also collected into serum separating tubes and tubes containing fluoride oxalate, and allowed to clot on ice before being centrifuged for seven minutes at 5000g and 4˚C. Aliquots of serum and plasma were frozen at -80˚C for later analysis of insulin and glucose respectively. Fasting, 30, 60, 90 and 120 minute plasma samples were analysed for glucose using the YSI 2300 Stat Plus analyser (Yellow Springs, USA) in duplicate

with a CV of < 1%. Corresponding serum samples were analysed for insulin using Millipore human insulin ELISA kits in duplicate with a CV of 10%. Insulin sensitivity was determined using glucose and insulin area under the curve (AUC) calculated by a computer-based trapezoidal model using GraphPad Prism 5 for Windows (Version 5.01, La Jolla, CA) and calculated using the oral glucose insulin sensitivity (OGIS) index [152].

5.3.3. Statistical analysis

All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of $p = 0.05$. Change scores for glucose and insulin response along with OGIS were calculated by subtracting the follow-up value from the baseline value. The mean change scores at each time-point were then compared with the predetermined [148] [Chapter 4] clinically meaningful change to determine its relevance. A repeated measures analysis of variance (ANOVA) was completed for nutritional components to determine change over time. Simple regression models were constructed to assess whether body composition variables measured through DXA, contributed to the changes experienced for glucose AUC, insulin AUC and OGIS. Data are presented as means (95% confidence intervals [CI]) unless otherwise indicated. Approximately 3% of data points were missing (due to occlusions within the cannula) and were substituted by bringing the last known value for that time-point forward [154] for 30 minute glucose and insulin (two and one occasions respectively), 60 minute glucose and insulin (one occasion), 90 minute glucose and insulin (three occasions) and 120 minute glucose and insulin (one occasion), ensuring that AUC was calculated from five time-points. On one occasion, the 60 minute sample of the baseline test was unable to be collected, resulting

in the AUC for that individual at that time being calculated on four time-points instead of five. Post-hoc power analysis was conducted using G*power 3.1 software.

5.4. Results

While being categorised as having normal glucose tolerance by the baseline OGTT, one individual was identified as having hyperinsulinaemia (130 < insulin < 200 pmol·L^{-1}) at baseline, with an additional participant identified as having extreme hyperinsulinaemia (insulin ≥ 200 pmol·L^{-1}) at baseline. The individual with hyperinsulinaemia experienced a potentially unfavourable reduction (64 ml·min^{-1}·m^{-2}) to insulin sensitivity, according to OGIS, 24 hours after exercise before returning to baseline and showing no additional change, while the individual with extreme hyperinsulinaemia experienced a beneficial increase to insulin sensitivity through OGIS of between 66 ml·min^{-1}·m^{-2} and 128 ml·min^{-1}·m^{-2} at all follow-up time-points. Based on the findings from Chapter 4, these two participants (one male and one female) were excluded from the analysis leaving all further results presented as N = 8.

The remaining (N = 8) participants characteristics are presented in Table 5.1. Briefly, these participants did not meet the criteria for clinical hypertension or hypercholesterolaemia and glycaemic control (HbA1c) did not reach the criteria for a diagnosis of type 2 diabetes. Included male participants' had a mean total body fat of 27.9% with a mean of 21.5 kg of fat mass and 55.7 kg of fat free mass while female participants' had a mean total body fat of 35.4%, a mean fat mass of 25.7 kg and a mean fat free mass of 44.7 kg, as determined through DXA. The mean glucose and insulin response (area under the curve) to the baseline OGTT and baseline insulin sensitivity estimated through OGIS index is presented in Table 5.1.

Based on the previously identified clinically important values by measuring the response to repeated, consecutive daily OGTTs [148] [Chapter 4], a potentially unfavourable and clinically meaningful increase in the insulin response was observed on each of the four days following the resistance exercise session (> 7,061 $pmol \cdot L^{-1} \cdot 120min^{-1}$; Figure 5.2). The glucose response also increased by to a clinically meaningful degree on the third day following exercise (> 63.5 $mmol \cdot L^{-1} \cdot 120min^{-1}$; Figure 5.3), resulting in a potentially unfavourable change. In regards to OGIS index, a potentially unfavourable and clinically meaningful decrease (> 1.2 $ml \cdot min^{-1} \cdot m^{-2}$; Figure 5.4) was observed on all four days following the resistance exercise session. Simple regression modelling indicated that body composition variables did not contribute to the change in glucose AUC ($p = 0.905$; $R^2 = 0.119$), insulin AUC ($p = 0.717$; $R^2 = 0.262$) and OGIS ($p = 0.820$; $R^2 = 0.187$).

Analysis of food diaries revealed that baseline mean (95% CI) values for intake of energy, protein, fat and carbohydrate were 8228 kJ (7349.5 to 9106.4), 83.2 g (67.6 to 98.8), 72.0 g (57.5 to 86.5) and 218.7 g (183.9 to 253.4) respectively. Repeated measures ANOVA with a Bonferroni adjustment indicated no significant differences ($p = 0.56$) across the intervention days.

5.5. Discussion

The major finding from this study was insulin sensitivity may be adversely affected for up to four days following a single unaccustomed resistance exercise session and that this is independent of body composition. This is in contrast to previous findings of improved insulin sensitivity following a single bout of resistance exercise in young healthy untrained individuals [63, 64], young strength trained individuals [61], and older

individuals with T2D [62, 63]. Indeed, our results do concur with those that have shown no improvements to insulin sensitivity following an acute bout of resistance exercise [65, 66, 68]. Although, studies that have reported beneficial changes have generally involved individuals with poor glycaemic control, which may highlight the inability to improve something that is already functioning adequately [158].

The findings from this study tend to suggest that a single session of unaccustomed resistance exercise may actually result in increased insulin production to maintain glucose homeostasis, or being in a previously theorised state of transient insulin resistance [159]. It is therefore important to look at mechanisms for why this may occur as a previous study of acute aerobic exercise in trained older individuals reported a beneficial increase to insulin sensitivity, for three but not five days [160] in comparison to the inactive individuals who completed resistance exercise in this study. Therefore it may be that the exercise mode is important, since unfamiliar resistance exercise induces muscle damage that has been linked to increased concentrations of circulating pro-inflammatory cytokines such as tumour necrosis factor alpha [159]. Aerobic type exercise (consisting of mainly concentric muscle contractions) does not typically induce the same amount of muscle damage, nor the same increase in pro-inflammatory cytokines [161]. The glycaemic control and mechanisms for maintaining glucose homeostasis (hyperglycaemia) appears to also be important with the acute aerobic exercise data [160] suggesting that it may be necessary for people who already have good glycaemic control, to undertake a period of regular ongoing training to enable the working muscles to become responsive to the exercise stimulus and observe beneficial improvements to insulin sensitivity that have been shown following regular resistance training [162].

Table 5.1: **Participant Demographics**

Outcome Measure	Mean ± SD
Male / Female	2 / 6
Age (years)	51.5 ± 6.3
Weight (kg)	74.1 ± 11.2
Height (cm)	170.1 ± 4.5
BMI ($kg \cdot m^{-2}$)	25.7 ± 4.2
Waist:Hip	0.83 ± 0.07
SBP (mm Hg)	122 ± 13
DBP (mm Hg)	73 ± 10
Cholesterol ($mmol \cdot L^{-1}$)	5.0 ± 1.0
LDL ($mmol \cdot L^{-1}$)	2.9 ± 0.4
HDL ($mmol \cdot L^{-1}$)	1.54 ± 0.53
Triglycerides ($mmol \cdot L^{-1}$)	1.2 ± 1.0
HbA1c (%)	5.5 ± 0.2
Glucose ($mmol \cdot L^{-1}$)	4.9 ± 0.5
Insulin ($pmol \cdot L^{-1}$)	73.3 ± 43.1
Activity ($MET\text{-}min \cdot wk^{-1}$)	968 ± 1053
Sedentary Time (min)	368 ± 126
Bench Press 1RM (kg)	35.3 ± 13.1
Leg Press 1RM (kg)	115.6 ± 27.2
Shoulder Press 1RM (kg)	24.1 ± 9.2
Calf Raise 1RM (kg)	225.6 ± 70.7
Lat Pull-down 1RM (kg)	27.5 ± 10.0
Glucose AUC ($mmol \cdot L^{-1} \cdot 120min^{-1}$)	762.2 ± 185.9
Insulin AUC ($pmol \cdot L^{-1} \cdot 120min^{-1}$)	50,634.5 ± 26,128.7
OGIS index ($ml \cdot min^{-1} \cdot m^{-2}$)	439.3 ± 82.7

Data excludes that from the individuals with hyperinsulinaemia. BMI = body mass index; DBP = diastolic blood pressure; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MET = metabolic equivalents; SBP = systolic blood pressure; AUC = area under the curve; OGIS = oral glucose insulin senstivity

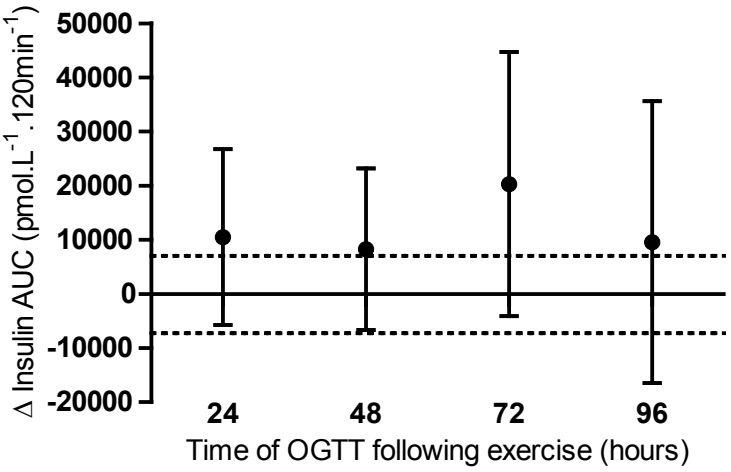

Figure 5.2: Insulin response to a single session of resistance exercise over four days.
Change from baseline of insulin response (AUC) following exercise. Mean and 95% CI for eight included participants. Broken lines represent the cut-points for a clinically meaningful change. Increase greater than 7061 pmol·L^{-1}·$120min^{-1}$ and a decrease greater than 7237 pmol·L^{-1}·$120min^{-1}$

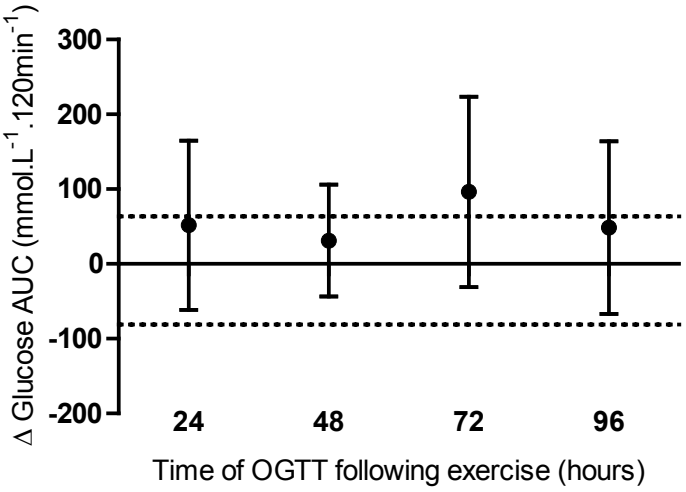

Figure 5.3: Glucose response to a single session of resistance exercise over four days.
Change from baseline of glucose response (AUC) following exercise. Mean and 95% CI for eight included participants. Broken lines represent the cut-points for a clinically meaningful change. Increase greater than 63.5 mmol·L^{-1}·$120min^{-1}$ and a decrease greater than 80.9 mmol·L^{-1}·$120min^{-1}$

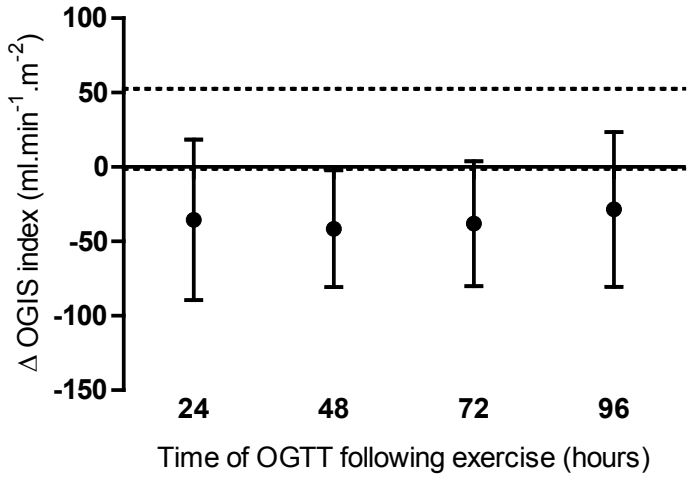

Figure 5.4: Insulin sensitivity response to a single session of resistance exercise over four days.
Change from baseline of OGIS index following exercise. Mean and 95% CI for eight included participants. Broken lines represent the cut-points for a clinically meaningful change**.** Increase greater than 52.7 ml·min^{-1}·m^{-2} and a decrease greater than 1.2 ml·min^{-1}·m^{-2}

While two individuals with hyperinsulinaemia were excluded from this analysis of healthy individuals, their individual results were noteworthy. The individual with extreme hyperinsulinaemia (insulin $\geq$ 200 pmol·L^{-1}) appeared to experience large beneficial increases in insulin sensitivity while the individual with a lower level of hyperinsulinaemia (130 < insulin < 200 pmol·L^{-1}) seemed to experience larger unfavourable reductions in insulin sensitivity. While individuals with hyperinsulinaemia have not specifically been referred to in the literature, it could be reasonably assumed that individuals with type 2 diabetes would have some degree of hyperinsulinaemia given this is a mechanism to control glucose levels. Therefore, when comparing the results from these two individuals and those with type 2 diabetes from the published literature [62, 63], it is possible to cautiously suggest that individuals with sub-optimal levels of metabolic health may display different responses and responses of greater magnitude compared to individuals with normal glucose metabolism. This however, requires further

research in this specific population to elucidate why these differences may occur when compared to those individuals with insulin levels within the desirable range.

5.6. Conclusion

While considering the limitations of this study design with a small sample size and the absence of a control group to directly compare the results to, it can be concluded that a single bout of resistance exercise does not improve insulin sensitivity in apparently healthy individuals with good glucose homeostasis and may indeed have a potentially short-term adverse effect, proving the hypothesis correct. Post-hoc power analysis calculated an effect size of 0.88; and for our sample of eight with an alpha value of 0.05, the study appeared appropriately powered at 99%. However, further research is suggested to confirm these results. Potential issues have been identified for novice resistance training individuals to be aware of in the days immediately following resistance exercise. Further investigations into the training duration and frequency required before being able to observe known improvements to insulin sensitivity that occur from ongoing resistance training [162] are warranted. In addition, investigating the effect of a single session of resistance exercise in individuals at risk of, or with T2D is pertinent. These results pose further questions relating to the ability of ongoing resistance training to diminish the potentially adverse effects of acute resistance exercise and if this is the case, the length of time that training needs to occur for this to happen.

Chapter 6

An investigation into markers of insulin sensitivity and inflammation in response to a single session of resistance exercise in inactive individuals

6. An investigation into markers of insulin sensitivity and inflammation in response to a single session of resistance exercise in inactive individuals.

6.1. Preface

Following previous findings that a single session of resistance exercise may have a potentially adverse short-term effect on glucose tolerance and insulin sensitivity (Chapter 5), the question remained as to whether individuals with type 2 diabetes (T2D) respond to a single session of resistance exercise in a similar way to people without diabetes. Making this investigation more challenging however, was the previous finding that repeated oral glucose tolerance tests may not be appropriate to estimate insulin sensitivity in people with T2D [Chapter 4]. This chapter is based on a manuscript that has been submitted for peer-reviewed publication.

6.2. Introduction

Type 2 diabetes is a condition of chronic insulin resistance where the pancreas is unable to adequately increase insulin secretion to account for the decreased insulin action [29]. It has been linked with overweight and obesity, which has also been associated low-grade inflammation [35]. With the prevalence of T2D rapidly rising [18, 19], it is vital that appropriate treatment and prevention programs are established. Exercise is a key component of treating [4] and preventing [163] T2D, however a large proportion of the population fail to meet the recommended exercise guidelines [69], due to a perceived lack of time [157] along with a fear of falling, physical ailments and inertia specifically in older adults [164].

The effect of resistance training on diabetes has become a focus, through findings of improved glucose levels and insulin sensitivity [80, 91, 92]. Consequently, guidelines now strongly advise the completion of resistance training [51]. Additionally, higher intensity resistance training appears to provide greater benefit than lower intensity training, however the required frequency to maintain or continue these improvements remains unclear [70]. Responses to a single session of resistance exercise in apparently healthy individuals have produced equivocal findings, with reports of increased insulin sensitivity 24 hours after the session [64], and insulin action ~36 hours after unaccustomed eccentric resistance exercise [67], whilst others [66] suggest an impairment of insulin action and impaired insulin sensitivity that may last for up to four days [155] [Chapter 5]. In people with T2D, insulin sensitivity or glucose tolerance has been reported to be improved up to 24 hours following a single resistance exercise session [62, 63], but the number of studies is limited and further research is required.

Markers of inflammation in response to exercise have been investigated mainly in relation to aerobic type activity. When the response to a single session of resistance exercise has been investigated, it has typically been in healthy but not resistance trained individuals [147]. Leptin, resistin, tumour necrosis factor-alpha (TNF-α), C-reactive protein (CRP) and interleukin (IL)-6 are reported to be pro-inflammatory adipocytokines that impair insulin sensitivity while adiponectin and IL-10 are anti-inflammatory and enhance insulin sensitivity [165]. Long-term exercise interventions appear to promote reductions in inflammation which, unsurprisingly is influenced by the type of exercise [166]. However, after a single session of resistance exercise, there appears to be no change to TNF-α or CRP, and reductions to IL-6 are only observed in the immediate hours following exercise [147].

Therefore the aim of this study was to investigate the insulin sensitivity and inflammatory cytokine response over three days following a single session of moderate-high intensity resistance exercise in middle-aged adults with and without T2D. It was hypothesised that a single session of resistance exercise would improve insulin sensitivity in people with type 2 diabetes when compared with apparently healthy individuals.

6.3. Methods

6.3.1. Participants and study design

Ten inactive (not meeting aerobic physical activity guidelines), apparently healthy males (N = 3) and females (N = 7) and 10 inactive individuals with T2D (males N = 6, females N = 4) with a mean ± SD age of 56.7 ± 8.2 years, height of 170.3 ± 7.7 cm and body mass of 80.7 ± 13.1 kg were enrolled to participate. Ethical approval was granted from the Human Research Ethics Committees of RMIT University and Austin Health, and all participants provided written informed consent. This study conformed to the principles of the Declaration of Helsinki. Inclusion criteria were: aged 40-69 years, had not participated in resistance training in the last six months and were taking a stable dose of medications (if they were taking medications). Exclusion criteria included: recent coronary event or established heart disease, uncontrolled hypertension (> 150/90 mmHg), neuropathy, orthopaedic disorder preventing them from completing resistance exercise, any medical condition that contraindicated resistance exercise, and being unable to understand English or follow instructions. The 10 apparently healthy individuals reported in this study are the same 10 participants reported in Chapter 5, with the fasting samples

collected for each oral glucose tolerance test used for the analysis and insulin sensitivity calculated using homeostasis modelling assessment equations [120].

Following a 12-hour overnight fast, participants arrived at the research facility between 0600 and 0900 hours by private vehicle. They underwent dual x-ray absorptiometry (DXA) scanning (Lunar® DPX-IQ, GE Healthcare) for assessment of body composition. Height (QuickMedical stadiometer, to the nearest 0.1cm), body mass (Tanita, BWB-600, to the nearest 0.1kg) and blood pressure (NISSEI, DS-105E, Japan Precision Instruments Inc., Japan) were measured, and a fasting blood sample collected. Participants were then given a standardised breakfast (toast and juice) and were familiarised with the resistance exercise equipment. Participants completed one repetition maximum (1RM) testing on all exercises included in the resistance exercise session. One repetition maximum testing followed a set protocol as reported previously [63].

Following a minimum of a 7-day wash-out period, participants returned to the research facility following a 12-hour overnight fast and had a blood sample collected prior to consuming the standardised breakfast. Participants completed the progressive resistance exercise session consisting of three sets of 10 repetitions for five whole-body exercises (bench press, 45˚ leg press, shoulder press, 45˚ calf raises and lateral pull-down) at a load equal to 45%, 60% and 75% of their 1RM. The resistance exercise protocol was based on protocols used in similar previous research [63, 65]. Participants returned to the research facility after a 12-hour overnight fast to provide a blood sample on each of the next three days following the exercise session. The study protocol is presented schematically in Figure 6.1.

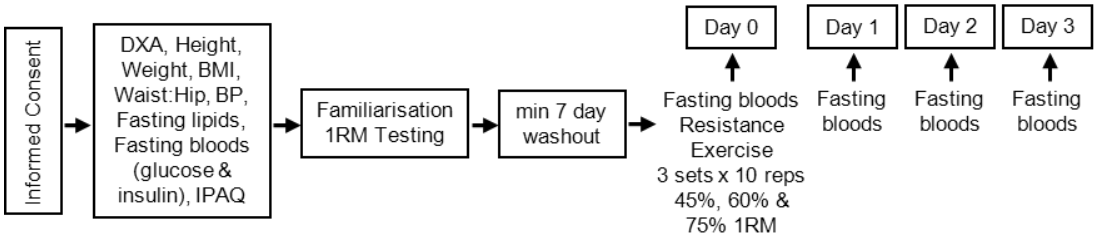

Figure 6.1: Study protocol.
DXA = dual x-ray absorptiometry; BMI = body mass index; BP = blood pressure; IPAQ = international physical activity questionnaire; reps = repetitions; 1RM = one repetition maximum

Participants completed the self-report International Physical Activity Questionnaire [144] prior to beginning the study. Prior to undertaking the resistance exercise session, participants were given an accelerometer (Actigraph GT1M, Actigraph, Pensacola, Florida) with instructions on how to wear it on the hip for the next three days. These data were analysed using ActiLife analysis software (v3.4.0, Actigraph, Pensacola, Florida) and enabled the researchers to determine whether participants had undergone any changes to activity patterns over the duration of the study, which may have impacted on their insulin sensitivity. Participants were also asked to record all food consumed throughout the study period in a food diary (with an example provided) and were instructed to replicate their diet before each visit. Nutritional analyses were conducted by the same researcher on the FoodWorks 2007 (Xyris software (Australia) Pty Ltd., xyris.com.au) dietary analysis computer program version 5, service pack 1, to compare total energy consumed and the intake (grams) of protein, fat and carbohydrate each day.

6.3.2. Blood analysis

Baseline fasting blood samples were collected in serum separator tubes and an EDTA containing tube. These were sent to a commercial laboratory for analysis of lipid profiles (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein

cholesterol and triglycerides with coefficient of variation's (CV) of 2%, 9%, 12% & 3.5% respectively) and glycated haemoglobin (HbA1c; CV = 3%). Additional samples were collected into serum separating tubes and tubes containing fluoride oxalate, and allowed to clot on ice before being centrifuged for seven minutes at 5000g and 4˚C. Aliquots of serum and plasma were frozen at -80˚C for later analysis of glucose, insulin, adiponectin, leptin, IL-6 and TNF-α. Plasma samples were analysed for glucose using the YSI 2300 Stat Plus analyser (Yellow Springs, USA) in duplicate (CV < 1%). Serum samples were analysed for insulin, adiponectin and leptin using defined human ELISA kits (Millipore Corporation, Billerica, MA, USA) and IL-6 and TNF-α using Quantikine ELISA kits (R & D Systems, Minneapolis, MN, USA) in duplicate (CV = 13.5%; 2.9%; 2.8%; 3.2% & 2.7% respectively). Insulin sensitivity (%S) and resistance (HOMA2-IR) were determined using the updated homeostasis modelling assessment (HOMA2) equations [120]. Insulin sensitivity was determined using HOMA2 equations as it is suggested that repeating oral glucose tolerance tests on multiple days may not be appropriate in people with T2D [148] [Chapter 4].

6.3.3. Statistical analysis

All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of p = 0.05. Independent t-tests (two-tailed) were conducted to assess the difference between the two groups at baseline. The covariates of physical activity and nutritional content were assessed by a mixed between-within multivariate analysis of variance (MANOVA). Data for insulin sensitivity were not normally distributed and therefore, log transformed prior to statistical analysis. Repeated measures (group x time) analysis of variance (ANOVA) were conducted for fasting glucose, fasting insulin, insulin sensitivity and insulin resistance to track the response

over 72 hours following exercise. A modified Bonferonni adjustment using the Holm procedure [167] determined alpha values required for statistical significance were 0.0125, 0.017, 0.025 and 0.05 for glucose, insulin, insulin sensitivity and insulin resistance respectively. When differences between groups were detected, two-way ANOVA's were conducted to assess whether differences remained across all four days. Repeated measures (group x time) ANOVA were also conducted for adiponectin, leptin, IL-6 and TNF-α to assess the response 24 hours following exercise, and modified Bonferonni adjustments were applied resulting in alpha values of 0.0125, 0.017, 0.025 and 0.05 for the above outcomes respectively. Data are presented as means ± standard deviation (SD) or means (95% confidence intervals [CI]) unless otherwise indicated. Post-hoc power was calculated for the primary outcome measure of insulin sensitivity using G*power 3.1 software with the repeated measures, within-between interaction test selected, with the within groups calculated as 30.3 units and the mean variance over time following the exercise intervention calculated at 2.5 units. This resulted in an effect size of 0.29 and for our sample of 20 individuals across two groups with four repetitions, using an alpha value of 0.025 and a correlation among the repeated measures of 0.5, overall power was calculated to be 77%.

One blood sample was unable to be collected 24 hours after exercise, and on one occasion technical difficulties meant no serum was obtained from the 72-hour sample. These values were substituted by bringing the last known value for that time-point forward [154]. In the instance of the 24-hour post resistance exercise sample not being able to be collected, this individual was excluded from the secondary analyses investigating the response of inflammatory markers, resulting in the T2D group being N = 9 for these analyses. Additionally, IL-6 was not able to be analysed for one apparently

healthy individual due to a lack of available serum, resulting in N = 9 for that analysis. There was a malfunction in recording the accelerometer data in one individual with T2D, therefore activity data were analysed with N = 9 for the individuals with T2D.

6.4. Results

Individuals' with T2D had been diagnosed for an average (range) of 7.5 (0.25 – 15.0) years. At baseline the individuals' with T2D were on average 10 years older ($p = 0.003$) had a body mass that was 12 kg greater ($p = 0.04$), and had a tendency to have a larger fat mass ($p = 0.08$) than those without diabetes (Table 6.1). Additionally, individuals with diabetes had lower amounts of total and low-density lipoprotein cholesterol and impaired glycaemic control (HbA1c), fasting glucose and insulin sensitivity (Table 6.1). Nine of the 10 individuals with diabetes were treated with oral hypoglycaemic medications with six treated with metformin alone, two treated with metformin in combination with a glicazide and one treated with metformin and a glitazone. Additionally, individuals with diabetes were being treated with statins (N = 9), aspirin (N = 4), anti-hypertensives (N = 4), proton-pump inhibitors (N = 3), diuretic (N = 1), anti-depressants (N = 1) and anti-uricaemic agents (N = 1). Six apparently healthy individuals were not using medications while the others were taking stable doses of anti-hypertensive (N = 2), statin (N = 1) and thyroid (N = 1) medications. None of the apparently healthy individuals were currently smoking; however one individual with diabetes was currently smoking, but refrained from smoking during the fasting period.

Table 6.1: Participant Demographics

Outcome Measure	Apparently Healthy Mean ± SD	Type 2 Diabetes Mean ± SD	p value
Male / Female	3 / 7	6 / 4	
Age (years)	51.6 ± 5.8	61.8 ± 7.2	0.003
Body Mass (kg)	74.7 ± 10.0	86.8 ± 13.4	0.04
Height (cm)	170.8 ± 7.9	169.7 ± 7.7	0.75
BMI ($kg \cdot m^{-2}$)	25.8 ± 4.5	29.6 ± 3.9	0.06
Fat Mass (kg)	25.8 ± 9.3	33.5 ± 9.4	0.08
Fat Free Mass (kg)	46.3 ± 6.6	49.9 ± 6.8	0.25
Percentage Fat (%)	35.3 ± 8.7	39.7 ± 6.7	0.22
SBP (mmHg)	120 ± 13	131 ± 20	0.17
DBP (mmHg)	74 ± 9	74 ± 8	0.88
Cholesterol ($mmol \cdot L^{-1}$)	5.1 ± 0.8	4.1 ± 0.6	0.01
LDL-C ($mmol \cdot L^{-1}$)	3.0 ± 0.4	2.1 ± 0.4	< 0.001
HDL-C ($mmol \cdot L^{-1}$)	1.53 ± 0.47	1.32 ± 0.22	0.22
Triglycerides ($mmol \cdot L^{-1}$)	1.2 ± 0.9	1.6 ± 0.6	0.24
HbA1c (%)	5.6 ± 0.3	6.8 ± 0.6	< 0.001
Glucose ($mmol \cdot L^{-1}$)	4.9 ± 0.5	7.6 ± 1.6	< 0.001
Insulin ($pmol \cdot L^{-1}$)	95.6 ± 84.9	137.9 ± 82.5	0.27
Insulin resistance (HOMA2-IR)	1.74 ± 1.51	2.75 ± 1.52	0.16
Insulin sensitivity (%S)	92.0 ± 67.9	45.5 ± 20.7	0.05
Activity ($MET\text{-}min \cdot wk^{-1}$)	987 ± 931	423 ± 256	0.09
Sedentary Time (min)	378 ± 142	468 ± 198	0.26
Bench Press 1RM (kg)	34.9 ± 11.7	33.2 ± 9.2	0.71
Leg Press 1RM (kg)	115.5 ± 24.2	97.8 ± 28.2	0.15
Shoulder Press 1RM (kg)	23.9 ± 8.3	15.6 ± 4.9	0.01
Calf Raise 1RM (kg)	214.5 ± 74.4	123.3 ± 39.8	0.004
Lateral Pull-down 1RM (kg)	27.8 ± 9.0	19.8 ± 4.3	0.03

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HbA1c = glycated haemoglobin; MET = metabolic equivalents; 1RM = one repetition maximum. Independent t-tests were conducted to assess the difference between groups at baseline.

On the day prior to completing the resistance exercise session, the mean ± SD total energy consumption for those with and without diabetes was 8,084 ± 1466 kJ and 8,154 ± 1102 kJ respectively. The breakdown of this for those with and without diabetes respectively was: 91.9 ± 31.3 g and 83.7 ± 19.2 g of protein; 71.4 ± 27.2 g and 68.9 ± 20.3 g of fat; and 213.4 ± 48.9 g and 221.6 ± 43.7 g of carbohydrate. Mixed between-within MANOVA revealed no statistical group by time interaction ($p = 0.33$) with no difference between groups ($p = 0.18$) or over time ($p = 0.70$) for diet. Individuals' with diabetes accrued an average ± SD of 123,719 ± 64,567 activity counts and recorded 8.2 ± 7.8 minutes of activity at a moderate intensity on the day of the resistance exercise intervention compared to those without diabetes accruing an average ± SD of 284,887 ± 109,509 activity counts and 29.2 ± 21.4 minutes of moderate intensity activity. There was no group by time interaction for variables of physical activity ($p = 0.25$) with no statistically significant change in activity over time ($p = 0.65$) and no statistical difference between groups ($p = 0.10$).

For the primary analysis, repeated measures ANOVA did not detect a statistically significant group by time interaction for glucose ($p = 0.27$), insulin ($p = 0.18$), insulin sensitivity ($p = 0.12$) or insulin resistance ($p = 0.15$). There were no time effects detected for any variable and no difference between groups for fasting insulin ($p = 0.10$). However, there were differences between those with and without diabetes for fasting glucose ($p < 0.001$), insulin sensitivity ($p = 0.018$) and insulin resistance ($p = 0.05$). Further analyses using two-way ANOVA revealed the fasting glucose values for those with and without diabetes were significantly different ($p < 0.001$) at all time points, however for insulin sensitivity and insulin resistance the differences were maintained for

two days post exercise before these variables became no longer statistically different between groups (Figure 6.2).

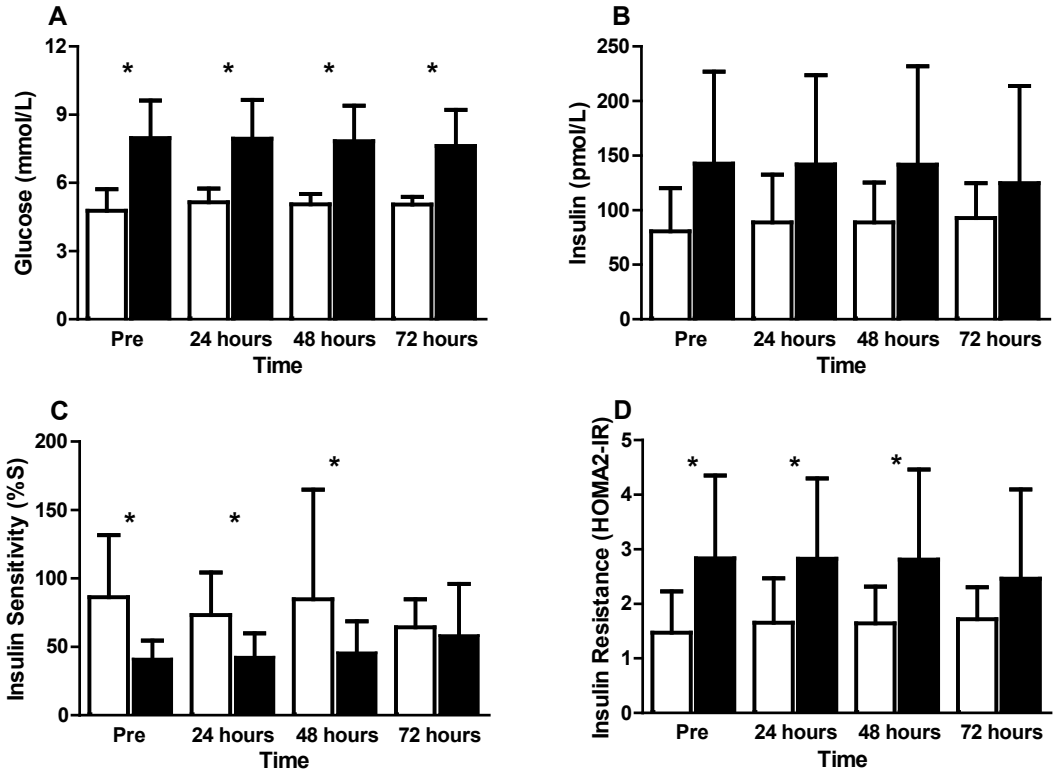

Figure 6.2: Metabolic response to a single session of resistance exercise in people with and without type 2 diabetes.
Response of fasting glucose (A), fasting insulin (B), HOMA2 insulin sensitivity (C) and HOMA2 insulin resistance (D) to a single session of resistance exercise in apparently healthy individuals (□) and individuals with type 2 diabetes (■). Pre is immediately before resistance exercise and 24 hours, 48 hours and 72 hours are all following resistance exercise. Bars are means with the standard deviation. * $p < 0.05$ between individuals with and without type 2 diabetes

In relation to the adipocytokines measured, adiponectin was detected in 95% of samples, with no adiponectin detected in one individual with diabetes either pre- or post-exercise. Leptin was detected in 100% of samples. Interleukin-6 was detected in 100% of samples pre-exercise but only 89% of samples post-exercise, with IL-6 not detected in two individuals with diabetes. Tumour necrosis factor-alpha was detected in 53% and 42% of samples pre- and post-exercise respectively, with one individual with diabetes and two apparently healthy individuals having TNF-α detected pre-exercise but not post-exercise

and one individual with diabetes having TNF-α detected post-exercise but not pre-exercise. For the secondary analysis, no group by time interaction was detected for the markers of inflammation: adiponectin ($p = 0.91$); leptin ($p = 0.42$); IL-6 ($p = 0.29$); and TNF-α ($p = 0.79$). There were also no time ($p > 0.05$) or group ($p > 0.05$) differences for any variable (Table 6.2).

Table 6.2: **Response of markers of inflammation to a single resistance exercise session. Mean ± SD**

	Pre-exercise	24 hours Post-exercise	p value[a]
Adiponectin (ng·mL^{-1})			
T2D (N = 8)	6.1 ± 6.6	4.7 ± 2.9	0.50
AH (N = 10)	12.1 ± 11.9	10.2 ± 14.7	0.51
p value[b]	0.22	0.31	
Leptin (ng·mL^{-1})			
T2D (N = 9)	23.1 ± 16.8	25.2 ± 14.3	0.37
AH (N = 10)	26.1 ± 26.9	24.6 ± 28.4	0.69
p value[b]	0.78	0.96	
IL-6 (pg·mL^{-1})			
T2D (N = 7)	5.8 ± 1.8	5.9 ± 2.3	0.75
AH (N = 9)	6.2 ± 2.2	5.6 ± 2.2	0.26
p value[b]	0.69	0.84	
TNF-α (pg·mL^{-1})			
T2D (N = 3)	2.6 ± 0.7	2.8 ± 0.7	0.80
AH (N = 4)	3.5 ± 1.3	3.4 ± 0.5	0.92
p value[b]	0.48	0.09	

T2D = type 2 diabetes; AH = apparently healthy individuals; IL-6 = interleukin-6; TNF-α = tumour necrosis factor-alpha. Paired t-tests were conducted to determine the change from pre- to post-exercise (p value[a]). Independent t-tests were conducted to compare groups both prior to and following resistance exercise (p value[b]).

6.5. Discussion

This study tracked the insulin sensitivity response to a single session of resistance exercise over three days in middle-aged individuals with and without T2D, along with assessing the response of adipocytokine markers of inflammation. The finding of no change to insulin sensitivity at any time, from 24 hours to 72 hours following resistance exercise is in contrast to previous findings from studies, using a similar resistance

exercise protocol, that reported improved insulin sensitivity 18 hours [63] and glucose tolerance 12-24 hours [62] after a single session of resistance exercise in people with T2D. These conflicting findings might be due to different methods of estimating insulin sensitivity (OGTT vs. HOMA2), or they may just indicate that improvements to insulin sensitivity following a single session of resistance exercise are a very acute phenomenon and therefore not detected in this study at 24 hours post exercise, suggesting that perhaps resistance exercise needs to be performed frequently, perhaps in excess of 2–3 times a week, to obtain metabolic health benefits. The lack of change, both in this study, and in a previous study of apparently healthy individuals [155] [Chapter 5], support this hypothesis that resistance exercise may need to be performed on an ongoing basis to observe changes to insulin sensitivity and glucose tolerance. However, it is interesting to note the significant difference in insulin sensitivity between those with and without T2D disappeared at 72 hours following resistance exercise. This appears to be due to small, non-statistically significant impairments in apparently healthy individuals and improvements in those with T2D, however the reasons for this are currently unclear and daily biological variation cannot be ruled out.

Impairments to insulin sensitivity following a session of resistance exercise have previously been considered to be due to transient insulin resistance caused by muscle damage increasing adipocytokines such as TNF-α [159]. There was no statistically significant impairment of insulin sensitivity or increase in insulin resistance in either of this study's population groups, nor were any markers of inflammation increased at 24 hours following the resistance exercise session.

Due to its insulin sensitising and anti-inflammatory effects [168], adiponectin has been reported to be an independent indicator of insulin sensitivity [169] with recent review articles indicating increases to adiponectin in most cases, following ongoing resistance training [165, 168]. Studies investigating a single session of aerobic exercise have provided equivocal results in terms of changes to adiponectin, however increased adiponectin concentrations have been reported immediately following a single session of resistance exercise only in people who had been regularly completing resistance training [170]. The findings in inactive and untrained individuals from the current study concur with the findings of others that no change to adiponectin concentration occurs in sedentary individuals and individuals who run but do not complete weight training [170].

No difference in leptin concentrations have been reported in trained and untrained individuals immediately following a single session of resistance exercise [170, 171]. Nindl and colleagues [172] also reported no change in the hours immediately after a resistance exercise session, however differences between the control and exercise interventions were found at nine, 10, 12 and 13 hours following the exercise protocol. This indicated that leptin responses to resistance exercise are delayed. However in the current study, in which leptin was assessed at a time point later than those of Nindl and colleagues [172], it was found that leptin was not changed at 24 hours after the resistance exercise session. This may be due to leptin not changing at any time in the current study or if it did, it returned to pre-exercise concentrations within 24 hours.

The response of IL-6 and TNF-α following a single session of resistance exercise are varied with reports of increased IL-6 on some occasions and no change on others, while typically TNF-α has remained unchanged [147]. Where increases have been observed in

IL-6, they have typically returned to baseline within 24 hours, although in one study they remained elevated for up to 72 hours [173]. The current findings add to the literature that no ongoing (at 24 hours) increase in IL-6 or TNF-α concentrations are observed following a single session of resistance exercise in inactive middle-aged individuals with and without T2D, suggesting that a lack of improvement in insulin sensitivity at that point in time, is not due to an increase in inflammation or transient insulin resistance.

6.6. Conclusion

While the findings of this study are limited by a small sample size and estimating insulin sensitivity through indices from fasting glucose and insulin concentrations, it is strengthened by the inclusion of adipocytokine markers of inflammation thought to be indicative of insulin sensitivity [174] along with vascular function [175]. Given these limitations, it can be concluded that insulin sensitivity and inflammation are not modified from a single session of unfamiliar resistance exercise between 24 hours to 72 hours after the session and suggest that if insulin sensitivity is modified, the response appears to be very acute (i.e. < 24 hours), failing to prove the original hypothesis. Given that significant differences in insulin sensitivity between those with and without T2D appear to be abolished 72 hours after the resistance exercise session, further research using methodologies that measure, rather than estimate insulin sensitivity and glucose tolerance, and/or sample frequently or continuously during free living conditions are justified to investigate whether these changes are significant and to determine the mechanisms behind them. Never-the-less, these results suggest that a single session of resistance exercise is not detrimental to metabolic health and that a lack of improvement is not a consequence of increased inflammation.

Chapter 7

An investigation into glucose control following single bouts of resistance and aerobic exercise

7. An investigation into glucose control following single bouts of resistance and aerobic exercise

7.1. Preface

Following findings of no change to insulin sensitivity using an estimate from fasting glucose and insulin levels or markers of inflammation following a single session of resistance exercise [Chapter 6], a method that measured glucose levels continuously was sourced to more rigorously examine glucose levels over a 24-hour period rather than using an approach that only captures a snapshot of time. A robust study design (randomised cross-over) was employed and it was decided to compare the responses between acute resistance and aerobic exercise. This chapter is based on a manuscript that has been submitted for peer-reviewed publication, which was completed in collaboration with a clinician from Austin Health and was possible thanks to funding received from the Australian Technology Network's Centre for Metabolic Fitness.

7.2. Introduction

It is generally accepted that adherence to guidelines for aerobic exercise by individuals with type 2 diabetes (T2D), is an appropriate and effective modality for improving their health status: and current guidelines recommend the completion of 150 $min \cdot wk^{-1}$ of moderate intensity aerobic exercise [4]. By comparison, there is a lack of consensus with regards to guidelines for undertaking resistance exercise to achieve optimal health in people with T2D [50, 52, 71]. And whilst previous research has indicated significant benefits associated with completing on-going resistance exercise, it appears that the current guidelines are based mainly on data obtained from apparently healthy populations, rather than individuals with T2D. It is therefore important that the acute impact as well as chronic effects of such exercise sessions are known, and the duration of

any changes to blood glucose levels established, so that specific guidelines can be defined and routinely prescribed to optimise health outcomes for people with T2D.

The development and publication of effective resistance exercise guidelines are of particular importance, given that many individuals with T2D may not be capable of achieving the amount, volume and intensity of aerobic exercise required for improving health [77, 124] and a large proportion of individuals with T2D fail to meet the current aerobic exercise guidelines [69]. Additionally, if resistance exercise produces different metabolic responses and/or works via different pathways to aerobic exercise [77], the implications of these differences need to be understood by researchers and clinicians.

Along with lifestyle modifications and the initiation of glucose lowering medications, current treatment recommendations for T2D advocate the early implementation of insulin therapy to achieve and maintain glycaemic control [4]. And given the increasing prevalence of T2D, it is likely that health professionals will need to care for more insulin treated people with T2D. It is therefore important to examine the effect of exercise on individuals with T2D being treated with insulin. Few studies to date [176, 177] investigating the effect of exercise on people with T2D have included those being treated with insulin. Consequently this investigation was performed in an attempt to provide more information regarding glucose response to exercise in this ever increasing sub-population of people with T2D.

Whilst it is known that exercise training improves insulin sensitivity in the long-term [74], literature regarding the immediate acute effects of exercise on insulin sensitivity and glucose tolerance are not as well defined [70]. Some clinical studies using animal models have investigated the acute effects of aerobic exercise [178-180] while in humans, results have indicated that a single session of low intensity aerobic exercise can reduce the mean 24-hour glucose concentration compared to no exercise, but high intensity aerobic exercise did not [181]. There are even fewer human studies investigating acute resistance exercise [62-66] and only three have specifically addressed this issue in people with T2D [62, 63, 177]. Results following these studies have been equivocal and an important limitation of all studies is a failure to determine the duration of improved insulin sensitivity following an acute bout of either resistance or aerobic exercise. Findings from aerobic exercise suggest that acute improvements in insulin sensitivity are likely to be localised to the exercised muscles through mechanisms such as glycogen depletion, along with improved contraction and insulin induced GLUT-4 (glucose transporters) translocation [182]. However, any mechanisms underlying an improvement in insulin sensitivity following an acute bout of resistance exercise have not been fully elucidated, although they are understood to have some common mechanisms to aerobic exercise along with some unique adaptations attributable to resistance exercise alone [70].

Individuals with T2D have been shown to have increased insulin sensitivity or glucose tolerance for 12-24 hours after a single bout of resistance exercise [62, 63], however our preliminary results suggest that no change to insulin sensitivity up to 72 hours following a single resistance exercise session is observed using the updated homeostasis modeling assessment equations. Limitations of small sample sizes and short follow-up periods are

apparent in studies of resistance exercise and similarly are also seen in studies evaluating acute aerobic exercise. All but two [177, 181] of these studies have used methods that provide a 'snapshot' approach to estimating insulin sensitivity or glucose tolerance. However, the relatively recent development and availability of continuous glucose monitoring (CGM) systems means that a more complete picture of the 24-hour response can be provided in comparison to the one-off 'snapshot' methods of fasting blood tests and oral glucose tolerance tests. Furthermore, whilst 'snapshot' methods have limitations in being able to detect and quantify the magnitude and duration of excursions into hyperglycaemia, these significant events can be easily identified and quantified through the use of CGM.

Therefore, the aim of this randomised, cross-over trial was to compare the glucose response, measured via CGM, after resistance and aerobic exercise; and secondly, to determine for what length of time any change to glucose tolerance remains following a single session of either exercise modality in inactive males with insulin treated T2D. It was hypothesised that a single session of resistance exercise would improve glucose control to a similar extent as that experienced following a single session of aerobic exercise.

7.3. Methods

7.3.1. Participants and study design

Ethical approval was granted from the Human Research Ethics Committees of RMIT University and Austin Health, and all participants provided written informed consent. This study conformed to the principles of the Declaration of Helsinki and was registered

with the Australia and New Zealand Clinical Trials Register (ACTRN12610000906055). Inclusion criteria were: aged 50-70 years, had not undertaken resistance training on two or more occasions per week over the last three months, were taking a stable dose of medications, were weight stable and had HbA1c values between 7.0% and 10.0%. Participants were excluded if they had been taking beta-blocking or oral hypoglycemic medications for less than six months, had impaired liver function, renal failure, severe retinopathy, recent coronary event or unstable cardiac disease, uncontrolled hypertension (> 180/90 mmHg), neuropathy or any medical condition that contraindicated resistance exercise. Participants were also required to be able to understand English or follow instructions.

The study design was a randomised cross-over trial, in which computer-generated concealed randomisation was used to allocate eight inactive (not meeting aerobic physical activity guidelines [53]) males with insulin treated T2D to complete either the aerobic or resistance exercise first. Once all baseline variables had been assessed and the participant had met all of the inclusion criteria, randomisation to which exercise session they would complete first, was achieved using individual opaque envelopes and administered by a person independent of the investigators. Participants' had a mean ± SD age of 61.0 ± 7.2 years, height of 173.9 ± 8.4 cm and body mass of 102.8 ± 35.4 kg (Table 7.1).

Participants were given a standardised meal to be consumed for dinner that contained 1,932 kJ of energy, 24.8 g of protein, 10.4 g of fat and 61.6 g of carbohydrate, the night before all visits. Participants arrived at the research facility each morning between 0600

and 0900 hours by the use of private vehicles, following a 12-hour overnight fast and had their height (stadiometer, QuickMedical®, USA; to the nearest 0.1 cm) and body mass (Tanita, BWB-600, Tanita Health Equipment H.K Limited, Hong Kong; to the nearest 0.1 kg) measured. Blood pressure was assessed using an automated blood pressure monitor (OMRON IA1B, OMRON healthcare Co. Ltd., Japan) before a fasting blood sample was collected. Each variable was measured in duplicate and in triplicate if a set tolerance threshold was reached, with the mean of duplicate values or median of triplicate values utilised. The coefficients of variation were < 1%, < 1% and 3% respectively for height, body mass and blood pressure. Participants were given a standardised breakfast (toast and fruit juice) and completed the self-report International Physical Activity Questionnaire [144]. Cardio-respiratory fitness was determined using an incremental exhaustive cycle protocol as reported previously [181] where the initial workload (Watts) was one Watt per kilogram of body mass and increased by 25% of the initial workload each 2.5 minute stage. Participants were required to maintain a cadence of 60-70 rpm for the duration of the test and oxygen uptake (VO_2) was measured throughout the test using an automated computerized breath-by-breath metabolic cart (ParvoMedics2400 Truemax, Parvomedics Inc., East Sandy, UT, USA). Peak oxygen uptake (VO_{2peak}) was defined as the maximum VO_2 measured on termination of the test without necessarily attaining the required parameters to be considered their physiological maximum. On two occasions, participants were unable to complete the initial workload, and therefore had the initial workload halved to enable them to complete the assessment. Participants were then familiarised with the resistance exercise equipment before undertaking one repetition maximum (1RM) testing on all six exercises to be included in the resistance exercise session. One repetition maximum testing followed a set protocol as reported previously [63].

Following a minimum of a 7-day wash-out period, participants returned to the research facility following a 12-hour overnight fast and had the CGM (Medtronics, iPro™2 professional model) inserted. The CGM consists of a microdialysis fibre (glucose sensor) that was inserted into the sub-cutaneous tissue in the lumbar region of the participants back (away from insulin injection sites) using a standard inserter (Sen-serter™), before connecting it to the recorder that sat on the skin surface immediately beside the glucose sensor. Participants were given a glucometer (Optium Xceed) to measure blood glucose values prior to each meal and before going to bed to calibrate the CGM. After consuming a standardised breakfast meal, participants were allowed to leave the research facility and return (again fasted) two days later to undertake either the resistance exercise session or the aerobic exercise session. Participants had a fasting blood sample collected, were given the standardised breakfast, and were instructed to take half of their normal insulin dose immediately prior to completing the exercise session. Apart from this, all medications were taken as prescribed by their physician. Following the exercise session, participants resumed their normal lifestyle for three days, during which time the CGM continued to record their blood glucose. Additionally they recorded time of food consumption, medication usage and glucometer derived blood glucose values. They then returned to the facility to have the CGM removed. Participants then resumed their normal lifestyle for two days, before repeating the protocol with the other exercise intervention. The study protocol is described schematically in Figure 7.1.

7.3.2. Exercise interventions

Both exercise interventions followed the exercise guidelines for people with type 2 diabetes [53, 55]. The resistance exercise session consisted of three sets of 8-10 repetitions for six whole-body exercises (bench press, 45˚ leg press, lateral pull-down, unilateral leg extension, seated row and unilateral leg curl) at 70% of 1RM with 60-90 seconds recovery between each set. The aerobic exercise session consisted of 30 minutes of cycling at 60% of VO_{2peak}, with breath-by-breath analysis conducted in three, five minute intervals throughout to ensure that the correct intensity was achieved and maintained. Activity levels throughout the study were assessed by accelerometer (Actigraph GT1M) with participants given instructions on how to wear it on the hip. These data were analysed using ActiLife analysis software (v4.4.1) and enabled the researchers to determine whether the participants had undergone any changes to their activity patterns within the duration of the study, which may have impacted their glucose tolerance.

7.3.3. Blood analysis

Baseline fasting blood samples were collected in a serum separator tube and an EDTA containing tube and sent to a commercial laboratory for analysis of lipid profiles (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C] and triglycerides [TG] with a coefficient of variation [CV] of 2.8%, 3.5% & 3.4% respectively, with low-density lipoprotein cholesterol [LDL-C] mathematically calculated from TC, HDL-C and TG), glycated haemoglobin (HbA1c; CV = 2.8%), glucose (CV = 2.8%), insulin (CV = 7.0%) and high-sensitivity C-reactive protein (hs-CRP; CV = 4.0%). Serum was allowed to clot at room temperature for 30-60 minutes before being centrifuged for 15 minutes at 3000g and 4˚C. Prior to each exercise session, a blood sample was collected in a serum

separator tube for analysis of glucose, insulin, and hs-CRP to ensure there were no lasting effects from the testing session or the previous exercise session.

7.3.4. Statistical analysis

A priori power calculation was based on the primary outcome of time spent in a state of hyperglycaemia, using estimates from the literature [177] where the minimally important change in the outcomes was three hours with a standard deviation of 11.95, an effect size of 0.26 was calculated. For the given effect size, an alpha value of 0.05, two groups completing four repetitions and a correlation among the repeated measures of 0.7, G*power 3.1 software recommended a sample size of 14 was required to achieve 80% statistical power. Given the cross-over design and allowing for 10% dropout, a sample of eight was recruited. All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of $p = 0.05$. One-way repeated measures analysis of variance (ANOVA) were completed to assess the change over time between, baseline and immediately prior to each exercise intervention for serum glucose, serum insulin and hs-CRP, with a Bonferonni adjustment, the value for significance was $p = 0.017$. A mixed between-within multivariate analysis of variance (MANOVA) was conducted to assess the physical activity variables of total counts and total steps in each 24-hour period before exercise and up to three days after exercise. A mixed between-within repeated measures (intervention x time) ANOVA was conducted for area under the 24-hour glucose curve and the percentage of each 24-hour time-period spent in a state of hyperglycaemia (glucose ≥ 10 mmol$\cdot L^{-1}$) to track the response over 72 hours following exercise. A Bonferonni adjustment was again used and this time the alpha value required for significance was 0.025. Due to a small sample size and for clinical application, the effect size was calculated for the change in amount of time spent in hyperglycaemia to

assess practical significance. Data are presented as means ± standard deviation (SD) or means (95% confidence intervals [CI]) unless otherwise indicated.

7.4. Results

Participant flow throughout the study is presented in Figure 7.1 with baseline demographics in Table 7.1. Briefly, participants' were on average overweight, borderline hypertensive and spent large amounts of time sitting. Their fitness and upper body strength were poor, while lower body strength was average [143]. They also had poor glycaemic control and low levels of HDL-C. One participant was currently smoking, but refrained from smoking during each fasting period. Of the eight participants, six were taking mixed insulin (Humalog Mix® = 3; NovoMix® = 3), and two individuals were taking both a long acting (Lantus®) and a short acting (NovoRapid®) insulin. All but one individual were taking oral hypoglycaemic medication along with the insulin, with five participants prescribed metformin monotherapy, one treated with dual therapy of metformin and a glitazone, and one taking a combination metformin and sulfonylurea medication. Participants were additionally treated with aspirin (N = 3), statins (N = 4), ACE inhibitors (N = 4), beta-blockers (N = 3), HMG-CoA reductase inhibitors (N = 2), angiotensin II receptor agonists (N = 2), diuretic, proton-pump inhibitor, calcium channel blocker and combination HMG-CoA reductase inhibitor and statin (all N = 1). There were no significant adverse events from completing either exercise intervention, however two individuals were unable to complete the 30 minute cycling protocol without frequent rest periods. All participants were able to complete the resistance exercise session as prescribed.

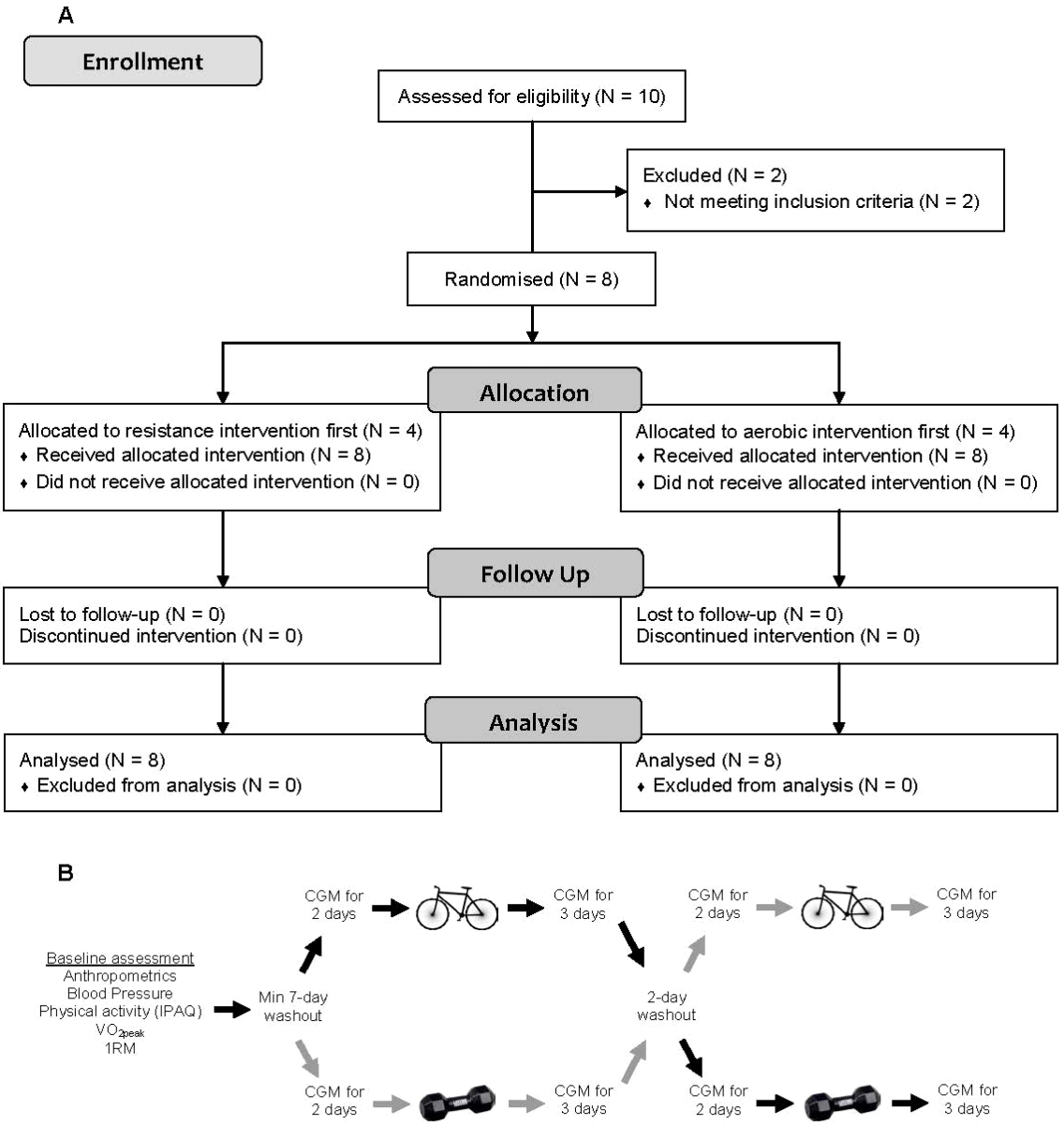

Figure 7.1: Participant flow through study (Consort diagram) (A) and study protocol (B).
IPAQ = international physical activity questionnaire; VO_{2peak} = peak oxygen uptake; 1RM = one repetition maximum; CGM = continuous glucose monitoring

Table 7.1: Participant Demographics

Outcome Measure	Mean ± SD
Diabetes (years)	18.0 ± 8.5
Age (years)	61.0 ± 7.2
Body Mass (kg)	102.8 ± 35.4
Height (cm)	173.9 ± 8.4
BMI ($kg \cdot m^{-2}$)	33.6 ± 9.4
SBP (mm Hg)	139 ± 19
DBP (mm Hg)	82 ± 8
Cholesterol ($mmol \cdot L^{-1}$)	3.9 ± 0.3
LDL-C ($mmol \cdot L^{-1}$)	2.2 ± 0.4
HDL-C ($mmol \cdot L^{-1}$)	1.00 ± 0.23
Triglycerides ($mmol \cdot L^{-1}$)	1.5 ± 0.7
HbA1c (%)	8.0 ± 0.3
Glucose ($mmol \cdot L^{-1}$)	8.4 ± 2.1
Insulin ($pmol \cdot L^{-1}$)	268.9 ± 528.2
C-peptide ($nmol \cdot L^{-1}$)	0.59 ± 0.55
hs-CRP ($mg \cdot L^{-1}$)	6.0 ± 8.0
Activity ($MET\text{-}min \cdot wk^{-1}$)	1683 ± 2524
Sedentary Time (min)	559 ± 311
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	19.8 ± 6.1
Bench Press 1RM (kg)	46.4 (15.2)
Leg Press 1RM (kg)	158.1 ± 49.8

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; HbA1c = glycated haemoglobin; hs-CRP = high sensitivity C-reactive protein; VO_{2peak} = peak oxygen uptake; 1RM = one repetition maximum

One-way repeated measures ANOVA between baseline and immediately prior to each exercise intervention failed to identify any significant difference for fasting serum glucose ($p = 0.05$), insulin ($p = 0.58$) and hs-CRP ($p = 0.34$) values. In the 24-hours prior to completing the resistance and aerobic training interventions respectively, participants' recorded an average of 186,428 ± 96,746 and 226,812 ± 104,531 counts and an average of 5,972 ± 3,154 and 7,499 ± 2,877 steps. Mixed between-within MANOVA revealed no difference between the interventions for the amount of physical activity completed ($p = 0.97$) and this did not change throughout either intervention ($p = 0.44$).

In the 24 hours immediately prior to completing resistance exercise and aerobic exercise, the mean (95% CI) glucose response (area under the curve [AUC]) was 187.4 (158.9 to 215.8) $mmol \cdot L^{-1} \cdot 24\text{-}hrs^{-1}$ and 186.7 (158.2 to 215.1) $mmol \cdot L^{-1} \cdot 24\text{-}hrs^{-1}$ respectively. Mixed between-within ANOVA detected a significant time effect ($p = 0.015$) for glucose AUC but no intervention by time interaction ($p = 0.29$). Pair-wise comparisons revealed that glucose AUC significantly increased ($p = 0.006$) in the first 24 hours following the exercise interventions (Figure 7.2) with a significant decrease ($p = 0.05$) returning to pre-exercise levels in the 48-72-hour time-period (Figure 7.2).

In the 24 hours prior to completing each exercise intervention, participants' spent an average (95% CI) of 23.0% (10.7% to 35.4%; 124 min to 533 min) and 27.0% (14.7% to 39.4%; 203 min to 574 min) of the time in a state of hyperglycaemia (glucose $\geq$ 10.0 $mmol \cdot L^{-1}$) before resistance and aerobic exercise respectively. Mixed between-within ANOVA failed to detect any time effect ($p = 0.11$) or intervention by time interaction ($p = 0.25$) for the amount of time spent in a state of hyperglycaemia (Figure 7.3). Despite no

statistically significant change being observed, there was a large practically significant change in the amount of time spent in a state of hyperglycaemia in the first 24 hours after each exercise intervention from the 24 hours before exercise with effect size (Cohen's d) calculated to be 0.98. In the periods of 24-48-hours and 48-72-hours after the exercise interventions, the practical significance of the change had reduced to a moderate level of d = 0.52 and d = 0.49 respectively.

7.5. Discussion

The major finding from this study was that glucose levels are elevated in the initial 24 hours following a single session of moderate intensity exercise in normally inactive individuals with insulin treated T2D. This finding is in contrast with previous research using CGM that has shown a single session of low intensity aerobic exercise reduced the 24-hour glucose response [181]. Furthermore, previous data indicates the 24-hour glucose response was not altered by a single session of low intensity resistance exercise followed by four short bouts of high intensity aerobic exercise [177].

The glucose response to exercise in young men with type 1 diabetes has previously been investigated by having participants perform 20 minutes of low to moderate intensity (40% VO_{2peak}) cycling and then either rest or complete a 10 second all-out sprint [183]. This exercise regimen showed that glucose levels continue to decline following moderate intensity cycling for participants that rested only, but remained stable in the group that completed the all-out sprint.

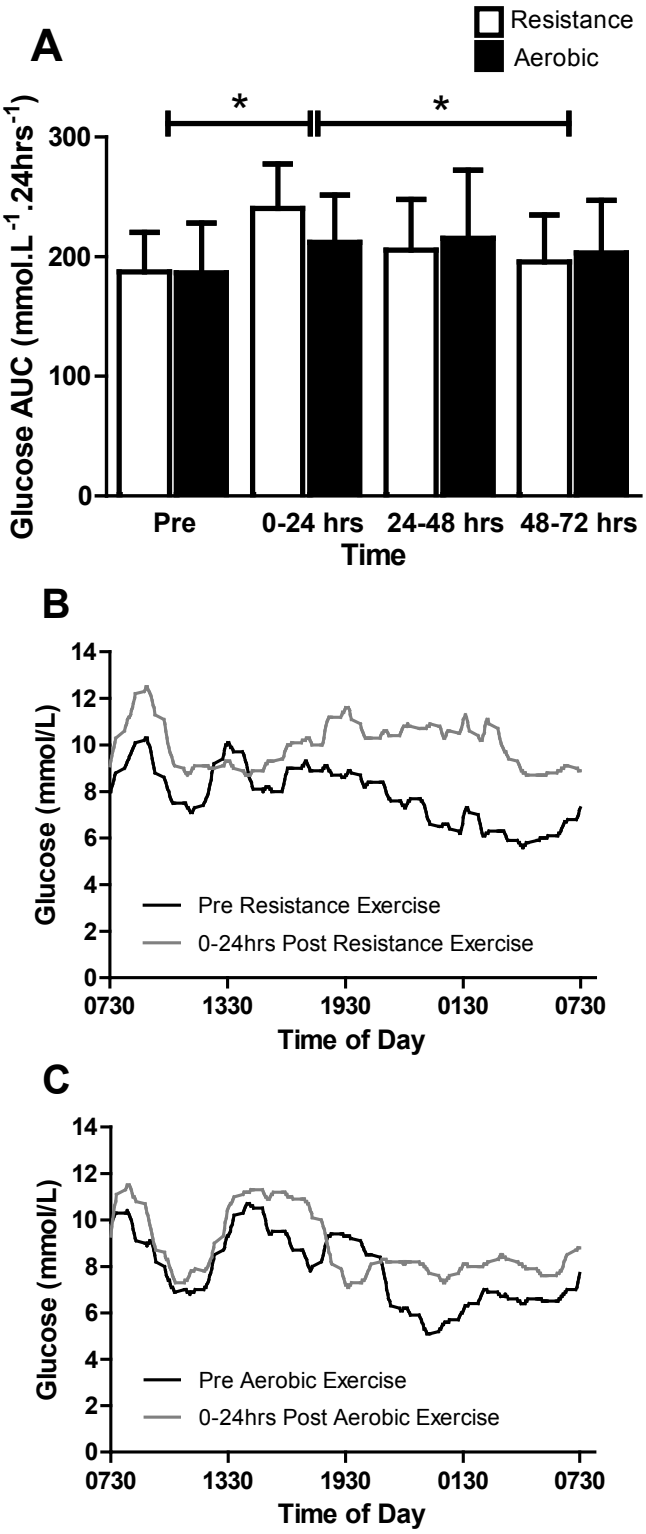

Figure 7.2: 24-hour glucose response to resistance and aerobic exercise.
The mean ± SD area under the 24-h glucose curve prior to and following resistance [white bars] and aerobic exercise [black bars] (A); the 24-h glucose response prior to [black line] and following [gray line] resistance exercise (B); the 24-h glucose response prior to [black line] and following [gray line] aerobic exercise. * $p < 0.05$

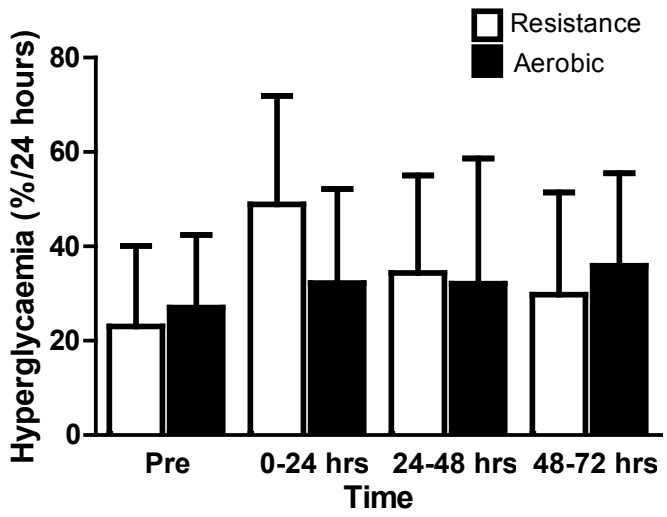

Figure 7.3: Hyperglycaemia in response to resistance and aerobic exercise.
The mean ± SD percentage of time within a 24-h period spent in a state of hyperglycaemia (blood glucose ≥ 10.0 mmol·L^{-1}) prior to and following resistance [white bars] and aerobic [black bars] exercise

The above study [183] and other similar studies involving people with T2D [177, 181] suggests that low intensity exercise could be most effective at reducing blood glucose levels following exercise. However, this approach is not reflected in the current exercise guidelines for individuals with diabetes [50, 52, 71]. The data from this study in which exercise was performed in accordance with current exercise guidelines, adds to the body of evidence that the volume and intensity of exercise described in this study results in a short-term impairment of the glucose response, as indicated by increased area under the glucose curve. And this may suggest that the current exercise guidelines are inadequate in terms of providing clinicians with information to optimise advice about the best way to manipulate insulin usage around periods of exercise in those that are novice exercisers.

The exact way that exercise influences insulin sensitivity and insulin resistance in T2D is yet to be precisely determined and subsequent changes in blood glucose levels remain unclear. These data does not support previous findings of increased insulin sensitivity (when calculated from a frequently sampled intra-venous glucose tolerance test) with no change to glucose effectiveness immediately following a single 20 minute aerobic exercise session in poorly controlled individuals with T2D [184]. However, these data do support findings of an attenuated exercise response from a previous study [185] that reported reduced muscle glycogen content with no change in AMPK phosphorylation following 40 minutes of low and moderate intensity aerobic exercise in well controlled individuals with T2D.

In those with T2D, insulin sensitivity and glucose tolerance, estimated through the use of an oral glucose tolerance test, has been reported to improve between 12 and 24 hours following a single session of moderate to high intensity resistance exercise [62, 63]. Further, a single session of low intensity resistance exercise followed by four 30 second bouts of high intensity cycling did not change the 24-hour glucose response, although the amount of time spent in a state of hyperglycaemia significantly reduced [177]. These findings could not be replicated with either resistance or aerobic exercise. By using CGM however, it was possible to identify that participants who undertook the exercise regimen according to current guidelines in this study, spent a prolonged period of time in a state of hyperglycaemia. This is information that cannot be identified using methods of 'snapshot' analysis, however the clinical implications surrounding the timing of medications and food consumption around exercise can be further investigated using CGM. Potentially it may even see the time of day at which exercise is completed become important.

The lack of any statistically significant change within fasting glucose, insulin and hs-CRP concentrations prior to either exercise intervention indicates that the washout period of seven days was appropriate and suggests that any changes to glucose or insulin from a single session of exercise have been abolished within this time frame. A cohort of working Australians has been reported to have completed an average of almost 9000 steps per day, with only approximately half of this sample meeting the physical activity guidelines [186]. Interestingly though, those who met the guidelines averaged approximately 9500 steps per day compared to the 8000 steps per day averaged by those who did not meet the guidelines [186]. Therefore the recorded average steps per day of between 6000 and 7500 in this study support the likelihood that these participants were indeed insufficiently active and not meeting the current physical activity guidelines [53]. Although the data is not shown, almost all of the activity measured by accelerometry in this study were recorded as being completed at a low intensity.

7.6. Conclusion

This randomised cross-over trial provides evidence that resistance exercise acutely (~24 hours) impairs glucose control; an outcome that was also observed following aerobic exercise in older male individuals with insulin treated T2D, proving the original hypothesis correct. While this study did not attempt to elucidate the mechanisms of how glucose tolerance is affected by exercise, the use of a device capable of monitoring glucose levels 24 hours a day, for several days and the study's randomised cross-over design, provide information that can be used to modify glucose altering treatment regimens and form the basis for further research. Further investigations are required to

determine: (i) whether females respond in a similar way to males; (ii) whether a similar glucose response occurs after multiple exercise sessions, and (iii) whether the glucose response is similar in individuals who are well trained in comparison to those who are inactive. While other health factors such as the cardiovascular response need to be considered when prescribing exercise to this population of at-risk individuals, it appears at least for the primary diabetes outcome of glucose tolerance that the current exercise guidelines require further refinement for untrained individuals beginning an exercise regimen.

Chapter 8

The effects of eight weeks of aerobic and resistance exercise training on insulin sensitivity and glucose tolerance in people with type 2 diabetes: A randomised controlled trial

8. The effects of eight weeks of aerobic and resistance exercise training on insulin sensitivity and glucose tolerance in people with type 2 diabetes: A randomised controlled trial

8.1. Preface

Following the series of acute investigations surrounding the effects of a single session of resistance exercise on insulin sensitivity and glucose tolerance [Chapters 5, 6 & 7] that all showed no change or a short-term impairment, it became clear that insulin sensitivity and markers of inflammation need a longer time course in which to respond and therefore should be investigated in response to a short-term exercise intervention. A randomised controlled trial was undertaken to compare the effects of resistance or aerobic training and a control condition (flexibility training) on insulin sensitivity and markers of inflammation. Although the most current exercise guidelines for type 2 diabetes recommend the completion of both aerobic and resistance type exercise [50, 58] this study was designed and commenced before the release of these guidelines, hence the comparison of the two modes and the lack of a combined exercise group. However, the most recent recommendation is based on limited studies that have evaluated the effect of combined training on metabolic health in people with type 2 diabetes [88, 99, 100], so should be examined further. The study described in the following chapter was completed in collaboration with researchers and clinicians at the Baker IDI Heart and Diabetes Institute and was made possible thanks to funding received from a Diabetes Australia Research Trust (DART) grant.

8.2. Introduction

Regular exercise is an essential component of type 2 diabetes (T2D) management, however most previous studies have concentrated on aerobic exercise. Only recently has

the benefit of resistance exercise in T2D been appreciated [82, 88]. Exercise is one of the cornerstones in the management of people with T2D [124] and it is currently recommended that people with T2D perform at least 150 minutes of moderate intensity aerobic exercise per week and, in the absence of contraindications, people with T2D are encouraged to perform resistance exercise two to three times per week [4, 55]. Even more recently the guidelines suggest that both forms of exercise be completed [50-52] however, the optimal exercise prescription in terms of type and frequency of exercise for improving insulin senstitivity in people with T2D is unknown.

Numerous studies have investigated the effects of aerobic type exercise on metabolic outcomes in people with T2D. Although this type of exercise has been reported to result in improved glycaemic control [75], recent studies of aerobic exercise have failed to show the same improvements [84, 99, 100, 187]. When aerobic and resistance exercise have been combined though, post-exercise blood glucose levels have been reported to continually reduce over a four-week program [122] and reductions in HbA1c have been observed when compared to a control group [84, 99]. The data are also equivocal in relation to insulin sensitivity with some studies showing increases in the rate of glucose disposal and the phosphorylation of glucose transporter-4 [187] and a 20%, but not statistically significant, increase in the glucose infusion rate [84], while insulin resistance estimated through the homeostasis modelling assessment (HOMA) has shown no change [100].

Resistance exercise has also been reported to result in improvements to insulin sensitivity and glucose tolerance 12-24 hours after a single session of resistance exercise in people

with T2D [62, 63] and following a period of chronic resistance exercise (6 weeks to 6 months) for between 48 hours [80] and 72-96 hours [90] after the final exercise session. Recently, a 12-week resistance training intervention has reported reduced insulin resistance, estimated through HOMA, and increased concentrations of adiponectin [100], however these changes were not statistically significant. Through their effects on carbohydrate and fat metabolism, the adipocytokines of adiponectin and leptin are believed to be surrogate markers of insulin sensitivity [146].

Despite the depth of positive evidence in relation to exercise and metabolic health and the strong recommendations to complete exercise as part of the treatment program in individuals with T2D [4], a large proportion of individuals with T2D do not complete the recommended levels [69]. Investigations regarding the minimal, most effective dose of exercise are required given a recent investigation of individualised lifestyle exercise prescription failed to increase either activity levels or glycaemic control [188]. The other major limitation of research to date is that insulin sensitivity following resistance training or aerobic training has not been tracked in people with T2D to determine the length of time that insulin sensitivity remains improved.

Given this, it was hypothesised that compared to a sham exercise (flexibility training) control group; there would be no difference in the change to insulin sensitivity after aerobic or resistance exercise training. Therefore, the primary aim of this study was to evaluate whether insulin sensitivity was improved following an 8-week period of resistance training or aerobic training with a secondary aim of evaluating the length of time that insulin sensitivity remained changed in people with T2D.

8.3. Methods

8.3.1. Participants and study design

Computer generated concealed randomisation was used to allocate participants to one of the three parallel arms (control vs. aerobic exercise vs. resistance exercise) in previously insufficiently active individuals with T2D by an independent, blinded investigator using opaque envelopes. It was not possible to blind participants to group assignment and due to resources, the same exercise physiologist who supervised the exercise training sessions, conducted the pre and post exercise assessments. Ethical approval for the study was obtained from the Human Research Ethics Committees of the Baker IDI Heart and Diabetes Institute and RMIT University and all participants gave written informed consent prior to any involvement in the study. This study conformed to the principles of the Declaration of Helsinki and was registered with the Australia and New Zealand Clinical Trials Register (ACTRN12609000799257).

A telephone-screening questionnaire, was used to identify potential participants who were 'insufficiently' active (less than 150 minutes of moderate intensity aerobic activity each week and not completing resistance exercise regularly more than once a week [53]). Volunteers then attended a screening visit to identify those eligible to participate and gave written informed consent prior to any measures being recorded. This screening process followed the guidelines published by the American College of Sports Medicine (ACSM) [143] detailing medical conditions that are contraindications to exercise participation. A physician reviewed all information collected during the screening process and completed a detailed medical assessment before providing the final approval of the person's suitability to participate. In addition, a letter with details about the

research project was sent to the participant's supervising doctor, requesting that medical treatment was not altered during the study unless medically required and that if this occurred, the researchers were informed.

Participants were included in the study if they met the following criteria: males or females aged 20-70 years with established T2D (longer than six months), treated with diet and/or oral hypoglycaemic medications, were stable in weight over the past three months (less than 5% change in body weight), had stable glycaemic control of at least eight weeks (no changes to medication) and HbA1c was between 6.5% and 9.9% at screening. Exclusion Criteria was: extremes of body mass index (< 18.0, > 40.0), seated resting blood pressure > 160 mmHg systolic or > 95 mmHg diastolic, pregnancy, anticipated requirement for medications affecting glucose tolerance during the trial, macroalbuminuria, proliferative retinopathy or severe neuropathy, renal disease or kidney failure, being a current smoker, taking medication to lower heart rate (beta blockers), unable to commit to completing the entire protocol, language other than English, known physical activity contraindications (following ACSM guidelines) and other illness/injury (acute or chronic) leading to physical or medical problems that may limit the ability to perform the necessary exercise. All data were collected at the Baker IDI heart and diabetes institute with the exception of the exercise testing which was completed at a public gymnasium, where the exercise interventions were also conducted.

Baseline measures were completed prior to randomisation to one of three interventions to be completed on three days each week for eight weeks. On the final session of the eighth week, participants completed their follow-up exercise assessments before returning to the

gym on the first scheduled session of the ninth week to complete their final exercise session. Participants then returned to the research laboratory two days (48 hours), four days (96 hours) and seven days (168 hours) after the final exercise session to have further assessments and blood tests completed. The study protocol is presented schematically in Figure 8.1.

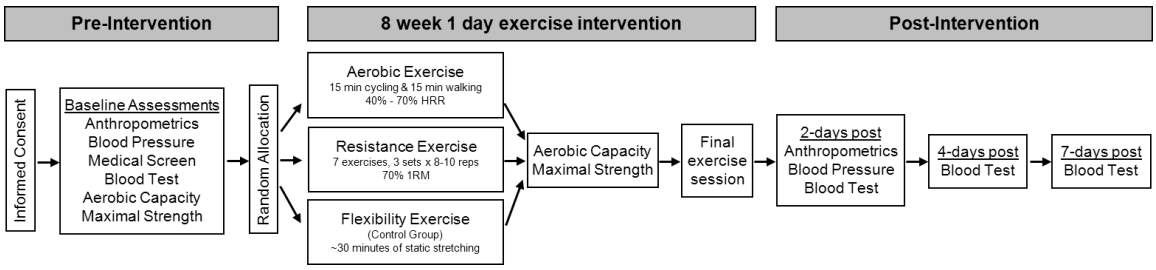

Figure 8.1: Study protocol
HRR = heart rate reserve; min = minutes; reps = repetitions; 1RM = one repetition maximum

8.3.2. Testing procedures

8.3.2.1. Anthropometrics

Basic anthropometric variables were assessed on the participant's initial visit. Height was measured using a wall mounted stadiometer (Surgical & Medical Products™, Model 1013522) to the nearest 0.1 cm. Body mass was measured to the nearest 0.1 kg on digital scales (Tanita BF-680W, Tanita Health Equipment H.K. Limited). Waist and hip circumference measurements were taken with a standard, non-elastic tape measure to the nearest 0.1cm according to ACSM guidelines [143]. Blood pressure was measured using a mercury sphygmomanometer listening for the first and last korotkoff sound through the brachial artery with a stethoscope. Each variable was measured in duplicate and in triplicate if a set tolerance threshold was reached, with the mean of duplicate values or median of triplicate values utilised. The coefficients of variation (CV) were < 1%, < 1%, < 1%, < 1%, 1.6% and 1.6% respectively for height, body mass, waist circumference, hip circumference, systolic blood pressure and diastolic blood pressure.

8.3.2.2. Aerobic Capacity

Aerobic capacity was measured via completion of a sub-maximal cycle test using the YMCA protocol [143] (up to four stages of three minutes). Participants were appropriately set up on the stationary cycle ergometer (Ergomedic 828E, Monark Exercise AB, Sweden) with a heart rate monitor (Polar F1™, Polar Electro Oy, Finland) applied around the chest for the continual measurement of pulse rate. Peak oxygen consumption (VO_{2peak}) was estimated via the use of standardised equations [143]. The YMCA protocol progresses intensity of the test according to the achieved heart rate of the participant at the completion of the first stage [143].

8.3.2.3. One Repetition Maximum Testing

Before completing the maximal strength testing, a familiarisation session was completed where participants were orientated to the exercise equipment to be used. All weights were removed to eliminate as much resistance as possible during this learning experience and participants completed 1-2 sets of 10 repetitions practising the lifting procedures and breathing techniques taught to them. On completing the familiarisation session, one repetition maximum (1RM) testing took place following a set protocol as reported previously [63]. The 1RM was used to establish the weight required to initiate the correct intensity for the resistance training program.

8.3.3. Exercise Intervention

The exercise interventions were matched as closely as possible for equivalent levels of energy expenditure through variations in the specific training session durations. To achieve this, it was identified that the metabolic equivalent (MET) intensity levels for

resistance training is three METs [189] and then the updated Compendium of Physical Activities [190] a universally accepted tool that lists specific physical activities by rate of energy expenditure (METs) was used to determine aerobic workloads. The proposed resistance training intervention consisting of 3.0 METs was estimated to take approximately 45 minutes to complete, equating in a total energy expenditure of 135 MET minutes (3.0 x 45). Moderate intensity aerobic exercise results in an intensity of 3-6 METs according to the Compendium [190]. In planning the aerobic exercise session, it was decided to use 15 minutes of cycling at 100 Watts (5.5 METs) and 15 minutes of walking on a treadmill at 4.8 $km \cdot h^{-1}$ (3.3 METs). This equated to a total energy expenditure for the aerobic exercise of 132 MET minutes ([3.3 x 15] + [5.5 X 15]). All participants were to attend three supervised exercise sessions per week at a public gymnasium with all exercise sessions (resistance, aerobic, flexibility) supervised by an accredited exercise physiologist.

8.3.3.1. Aerobic Training

Fifteen minutes of aerobic exercise using a stationary cycle followed by 15 minutes of walking on a treadmill at an intensity of 40-70% of heart rate reserve was completed, followed by 5-10 minutes of stretching as a cool down/recovery, for three sessions per week. This intensity is equivalent to the aerobic training guidelines provided by leading health agencies with regards to a moderate intensity walk [53]. Heart rate and rating of perceived exertion (RPE) using the Borg scale [191] were monitored every 7.5 minutes throughout the exercise session by the supervising exercise physiologist and used to guide the participant to achieve the prescribed intensity. Intensity was increased as needed to ensure that participants heart rates were in the desired range.

8.3.3.2. Resistance Training

An individualised resistance training program consisting of 7 whole-body exercises (bench press, 45° leg press, lateral pull-down, leg curl, shoulder press, triceps extensions and abdominal crunches) were completed using pin-loaded weight machines and free-weights. Three sessions per week were completed consisting of three sets of 8-10 repetitions at 70% 1RM followed by 5-10 minutes of stretching as a cool down/recovery. The weight lifted was progressively increased for each muscle group as tolerated once the prescribed number of sets of 10 repetitions was successfully achieved with appropriate technique on two consecutive sessions. One-repetition maximum testing was repeated after four weeks to establish a new baseline and to guide the prescription of training intensity within the prescribed range. Exertion levels were monitored using Borg's RPE scale [191]. The program was progressive in nature with only one set completed on the first session of training, two sets on the second session and three sets thereafter.

8.3.3.3. Controls

Participants were advised not to change their baseline activity level for the 8-week intervention and maintain all current medical intervention. To control for researcher interaction, control participants attended the gymnasium to complete 30 minutes of flexibility training three days per week.

8.3.4. Blood Analysis

Blood samples were collected following a 12-hour fast using a standard venepuncture procedure with samples collected at baseline and then again at two days (48 hours), four days (96 hours) and seven days (168 hours) following the final exercise session. Blood

samples were collected in a serum separating tube and allowed to clot at room temperature for 30 minutes before being centrifuged at 3000g for 15 minutes. Serum was separated then stored at -20°C before being transferred to -80°C until analysed for serum insulin, adiponectin, and leptin in duplicate using defined human ELISA kits (Millipore Corporation, Billerica, MA, USA) with a CV of 10%, 2% and 4% respectively. Samples were also sent to a commercial laboratory for the analysis of glycated haemoglobin (HbA1c), plasma glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides, within the same analyser. The Friedewald equation was used to calculate low-density lipoprotein cholesterol (LDL-C). Fasting insulin and glucose values were used to determine glucose tolerance and insulin sensitivity levels using the updated homeostasis modelling equations (HOMA2) [120].

8.3.5. Statistical Analyses

As this study was conducted in collaboration with a group of researchers from the Baker IDI heart and diabetes institute, the sample size was calculated for a primary outcome of endothelial function, and was based on results from Maiorana et al. [192], where the absolute difference in means for flow mediated dilatation was 3.3%. Therefore, based on detection of a 2% absolute change in flow mediated dilatation and a standard deviation of the change of 1.5%, 80% power and alpha of 0.01 and with consideration of the three parallel arm study design, a minimum of 14 participants per arm were required. Power calculations based on the study outcome of insulin resistance based on previous data using similar methodology [89, 91] where the absolute mean difference in the means 8% and the standard deviation of the change 3%. Using this data, an effect size of 0.2 was calculated, with an alpha level of 0.05 and 80% power and with consideration for three groups and four repeated measures G*power 3.1 software indicated that a total sample

size of 45 participants was required. This study was not powered, nor designed, to detect a difference between genders. Allowing for drop-outs recruitment was aimed at 16 participants per group.

One-way analysis of variance (ANOVA) with a Tukey post-hoc analysis was conducted to assess baseline differences between groups. Repeated measures (intervention by time) multivariate analysis of variance (MANOVA) were conducted separately for blood pressure variables (systolic and diastolic), lipid profiles (TC, TG, HDL-C and LDL-C) and fitness variables (estimated VO_{2peak}, bench press 1RM and leg press 1RM). Changes to glycaemic control (HbA1c), fasting glucose, fasting insulin, insulin sensitivity (HOMA%S), insulin resistance (HOMA2-IR), adiponectin and leptin were assessed using repeated measures (intervention by time) ANOVA. Further, simple and stepwise regression models were constructed to assess the relationships of change (post minus pre) in metabolic and adipocytokine variables that were found to have either significant group by time or time interactions with fitness variables of aerobic capacity and strength. All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of $p = 0.05$. Effect sizes to report practical significance were calculated as the change from the intervention subtracted from the change in the control divided by the standard deviation of the change from the control. Where the two interventions where compared, the aerobic training intervention was used as the control. Data are presented as means ± standard deviation (SD) or means (95% confidence intervals [CI]) unless otherwise indicated. The analysis was conducted as intention to treat with missing data points substituted by bringing the last known value for that outcome forward [154]. Data needed to be substituted due to participants being unable to attend the follow-up visit at two days (N = 1), four days (N = 3) and seven days (N = 1),

with a technical difficulty obtaining serum from the blood sample of one participant four days after the final exercise session.

8.4. Results

Participant flow through the study is presented in Figure 8.2. Briefly, 38 participants were randomised into one of the three study arms, however Kolmogorov-Smirnov normality tests revealed that baseline levels of glucose ($p = 0.003$), insulin ($p = 0.028$), HOMA%S ($p < 0.001$), HOMA2-IR ($p = 0.012$), leptin ($p < 0.001$) and adiponectin ($p = 0.017$) were not normally distributed. These variables were log-transformed and further analysis identified one individual from the resistance training group to be an outlier (greater than two SD from the mean) for glucose and another individual from the resistance training group to be an outlier for fasting insulin along with insulin sensitivity and resistance. Therefore, these two individuals were excluded from the analysis and data from 36 individuals were analysed. All pre and post exercise values for the above metabolic variables were subjected to log transformation prior to statistical analysis. The participants' had an average ± SD age, height and body mass of 59.4 ± 7.6 years, 1.69 ± 3.85 m and 92.6 ± 16.1 kg respectively and they had been diagnosed with diabetes for an average ± SD of 6.4 ± 3.9 years (Table 8.1). Of the 36 individuals, 27 were taking metformin with six of these taking metformin along with a DPP-4 inhibitor. Three additional participants were taking a combined DPP-4 inhibitor and metformin medication. Four individuals were taking no medications for any medical conditions, 23 participants were prescribed medications for blood pressure, with 23 also prescribed medications for cholesterol. Aspirin was prescribed for eight individuals. All data was collected between October 2009 and December 2010, with the trial ending due to funding running out to maintain staff to collect data.

One-way ANOVA revealed that baseline participant demographics were similar between groups with the exception of body mass ($p = 0.05$), where Tukey post-hoc analysis revealed that the flexibility group was significantly heavier than the aerobic exercise group ($p = 0.04$), (Table 8.1). One person completed all baseline testing and the first week of the control intervention before suffering the flu and extreme shortness of breath unrelated to the study, and was unable to complete any more of the intervention or the follow-up exercise tests. They did however, return for follow-up assessment at two and four days after their intervention was scheduled to be completed, but did not attend for the seven day follow-up testing. One individual from the resistance exercise group was not able to complete the follow-up leg press 1RM due to an injury sustained outside of the supervised exercise program. Overall, participants complied to the intervention with an average ± SD of 87% ± 20% of sessions completed with no difference in compliance rate between groups ($p = 0.23$). Average ± SD compliance rates for the resistance training group, aerobic training group and flexibility group were 88% ± 18%, 92% ± 9% and 79% ± 28% respectively. A total of four participants (3 completing flexibility training and 1 completing resistance training) completed less than 75% of the scheduled sessions.

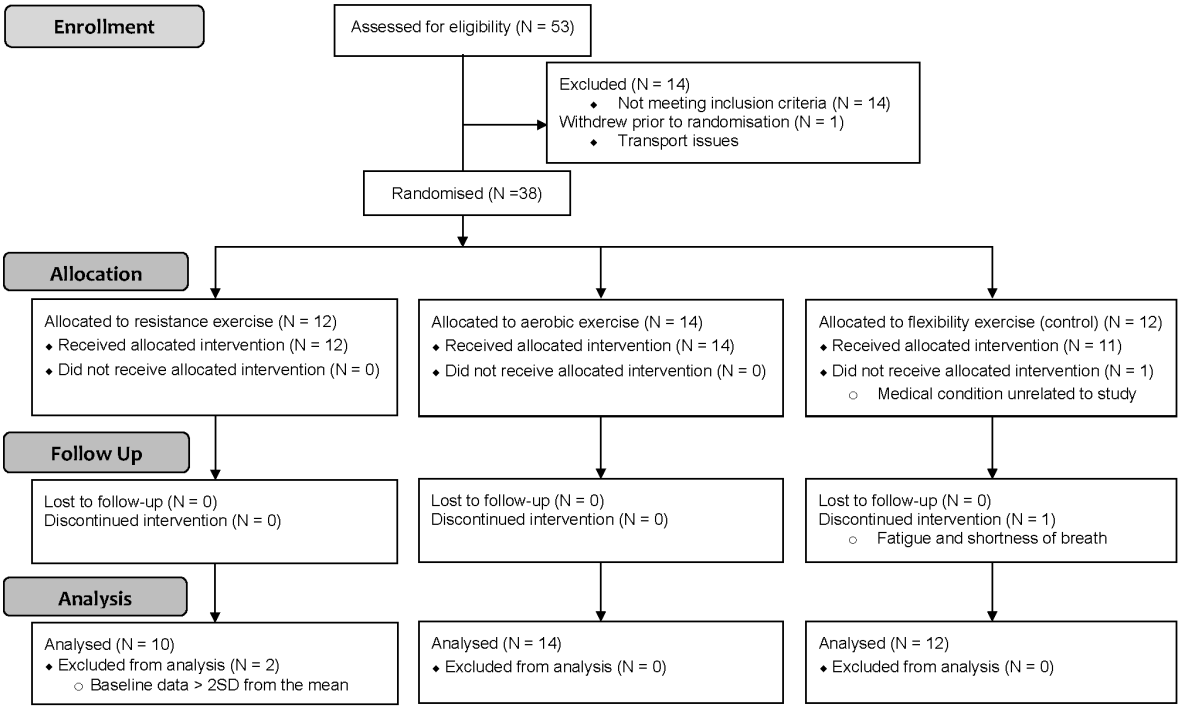

Figure 8.2: Participant flow through study (Consort diagram)

Repeated measures MANOVA for lipid profiles revealed no intervention by time interaction ($p = 0.86$) with no effect over time ($p = 0.94$) or between groups ($p = 0.44$). Repeated measures ANOVA also revealed no intervention by time interaction for HbA1c ($p = 0.63$), which also did not change significantly over time ($p = 0.86$). Repeated measures MANOVA for systolic and diastolic blood pressure revealed no intervention by time interaction ($p = 0.11$) but did identify a change over time ($p = 0.03$), which pair-wise analysis revealed was for a small (3 mmHg) increase in diastolic blood pressure ($p = 0.01$).

Mean RPE values throughout the aerobic exercise sessions were 12/20, while during the resistance exercise sessions they were reported as 16/20. Repeated measures MANOVA for variables of fitness, being estimated VO_{2peak} and upper and lower body strength,

revealed a significant intervention by time interaction ($p < 0.001$). Univariate analysis confirmed these intervention by time interactions for strength (upper body, $p = 0.001$ and lower body, $p < 0.001$) but not for VO_{2peak} ($p = 0.22$). Figure 8.3 shows the resistance training group experienced a 19% and 22% increase in bench press and leg press strength respectively compared to a 3% increase in bench press strength for both the aerobic training and flexibility groups along with a 4% increase and a 3% decrease in leg press strength for those in the aerobic training and flexibility groups respectively over the 8-week intervention. Despite being no intervention by time interaction for VO_{2peak}, there was a significant time effect ($p = 0.005$) where the aerobic training, resistance training and flexibility groups experienced a 16%, 6% and 5% increase respectively (Figure 8.3).

Table 8.1: Baseline participant demographics. Mean ± SD

Outcome	Resistance		Aerobic		Flexibility	
	Pre	Post	Pre	Post	Pre	Post
N (M/F)	10 (8/2)		14 (7/7)		12 (8/4)	
Age (years)	60.3±6.2		60.4±6.9		57.4±9.5	
Diabetes (years)	4.8±4.2		7.2±3.7		6.8±3.7	
Height (m)	1.69±0.09		1.67±0.09		1.72±0.11	
Weight (kg)	92.3±18.0	93.1±19.0	85.6±12.1	84.7±11.8	101.0±15.8*	100.0±15.9*
BMI ($kg \cdot m^{-2}$)	32.1±5.2	32.4±5.4	30.9±4.1	30.6±4.0	34.4±6.7	34.0±6.2
SBP (mmHg)	129±13	132±13	133±11	128±10	131±18	133±16
DBP (mmHg)	78±10	83±9	78±8	79±8	81±6	81±8
HbA1c (%)	7.2±0.7	7.4±0.7	7.7±0.9	7.7±1.1	7.3±0.7	7.2±0.5
Total Cholesterol ($mmol \cdot L^{-1}$)	4.6±1.4	4.3±1.1	4.5±0.6	4.4±0.8	4.5±1.1	4.6±1.0
Triglycerides ($mmol \cdot L^{-1}$)	1.6±1.1	1.4±0.9	1.6±1.0	1.5±0.5	1.8±0.7	1.9±0.7
HDL-C ($mmol \cdot L^{-1}$)	1.28±0.26	1.30±0.20	1.26±0.21	1.26±0.19	1.25±0.29	1.24±0.22
LDL-C ($mmol \cdot L^{-1}$)	2.6±1.3	2.4±1.0	2.5±0.7	2.4±0.7	2.4±1.1	2.5±0.9
Glucose ($mmol.L^{-1}$)	7.8±1.5	7.1±1.0	8.1±1.8	7.7±2.0	7.5±1.4	7.8±1.4
Insulin ($pmol \cdot L^{-1}$)	107.8±59.4	110.0±50.0	92.7±51.4	89.9±49.4	121.6±57.6	126.6±67.2
Insulin Sensitivity (HOMA%S)	62.1±38.1	55.4±27.4	62.4±25.3	66.8±26.9	50.5±25.8	46.6±18.9
Insulin Resistance (HOMA2-IR)	2.2±1.2	2.2±0.9	1.9±1.1	1.9±1.1	2.4±1.1	2.5±1.2
Estimated VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$)	25.7±3.5	27.1±6.2	25.6±6.7	29.7±8.2	24.7±5.8	26.0±9.1
Bench Press (kg)	50.3±16.9	59.8±21.9	39.4±17.4	40.7±16.4	42.1±22.7	43.3±21.9#
Leg Press (kg)	172.5±67.1	211.3±81.5	148.0±50.6	153.6±52.2	152.1±54.9	148.3±51.4*#
Leptin ($ng \cdot mL^{-1}$)	11.6±6.3	9.5±3.8	14.9±11.0	12.8±8.7	23.5±24.6	18.9±17.2
Adiponectin ($ng \cdot mL^{-1}$)	14.3±11.0	9.9±7.5	14.6±7.5	14.4±7.9	10.8±7.7	14.0±7.9#

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; VO_{2max} = maximal oxygen uptake; * $p < 0.05$ between groups, # $p < 0.05$ group x time interaction. Data for glucose, insulin, insulin sensitivity, insulin resistance, leptin and adiponectin was log transformed for statistical analysis but raw values are reported here for comparative purposes.

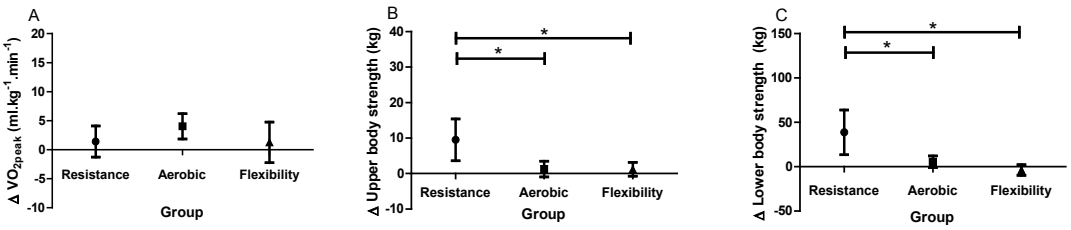

Figure 8.3: Change in fitness variables in response to 8 weeks of exercise.
Change from pre to post eight week exercise intervention for fitness and strength outcomes. Mean change with 95% CI. * $p < 0.005$.

Repeated measures ANOVA indicated no intervention by time interactions for fasting glucose ($p = 0.23$), fasting insulin ($p = 0.75$), insulin sensitivity ($p = 0.80$) or insulin resistance ($p = 0.83$). For fasting insulin, insulin sensitivity and insulin resistance there was also no statistically significant change over time ($p > 0.05$), however a time effect was found for fasting glucose ($p = 0.04$), where pair-wise analysis revealed a significant difference in glucose levels between two days after the final exercise session and seven days after the final exercise session ($p = 0.05$; Figure 8.4). While no statistical difference between the intervention and control groups for any of fasting glucose, fasting insulin, insulin sensitivity or insulin resistance were detected, there was a large practical change according to the effect size, between the resistance intervention and control (Cohen's d = 1.3) and the aerobic intervention and the control (Cohen's d = 1.1) two days after the final exercise session. At seven days after the final exercise session, there was no practical difference between the aerobic and control interventions (Cohen's d = 0.01), however a large difference remained between the resistance and control interventions (Cohen's d = 0.9). Between the two exercise interventions there were trivial and small differences at two days (Cohen's d = 0.14) and seven days (Cohen's d = 0.36) after the final exercise session respectively.

In respect to fasting insulin concentrations, the only practical change of note was a moderate change (Cohen's d = 0.63) between the aerobic intervention and the control seven days following the final exercise session, while interestingly, a similar change was observed between the two exercise interventions at the same time point (Cohen's d = 0.49). There was a small practical change noted between the aerobic intervention and the control (Cohen's d = 0.42) for insulin sensitivity two days following the final exercise session, which increased to a large change (Cohen's d = 1.03) seven days after the final exercise session, while a small change (Cohen's d = 0.47) was observed between the resistance intervention and control only at seven days after the final session. There were small differences in the change between exercise interventions at both time points. For insulin resistance a moderate change was noted (Cohen's d = 0.58) between the aerobic intervention and control only at seven days after the final exercise session.

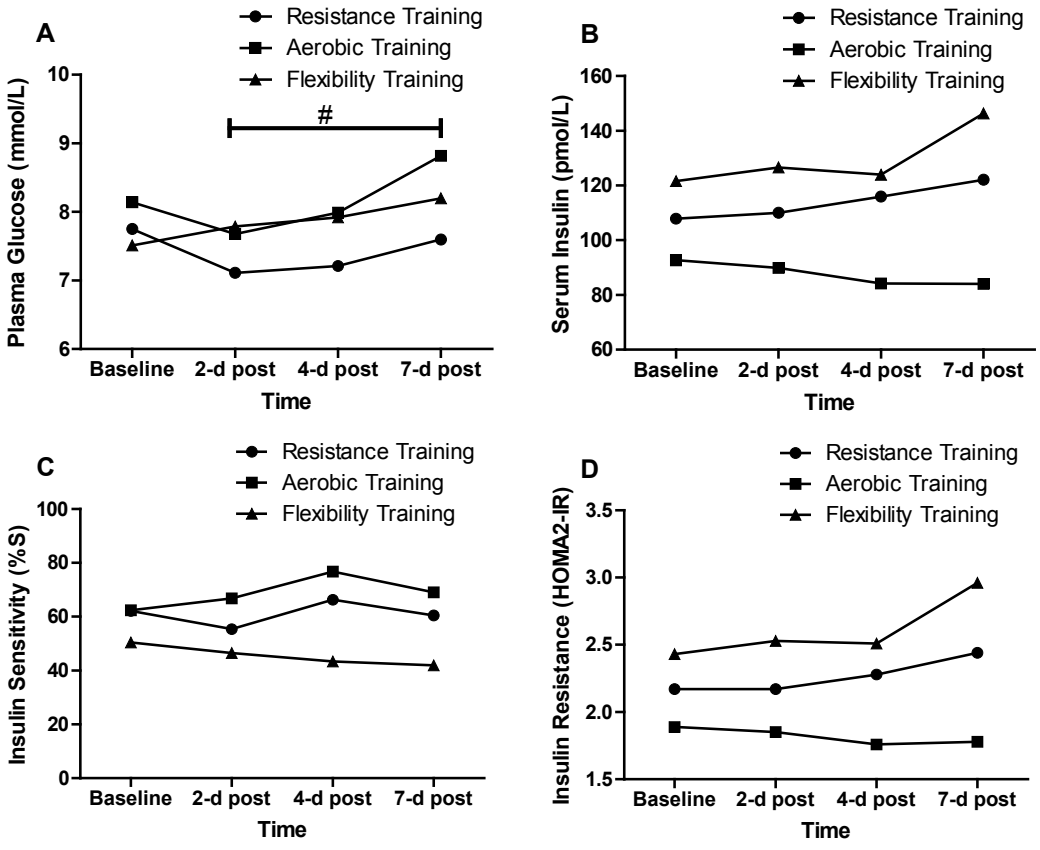

Figure 8.4: Glucose, insulin, insulin sensitivity & insulin resistance in response to 8 weeks of exercise. Mean values for fasting plasma glucose (A), fasting serum insulin (B), insulin sensitivity (C) and insulin resistance (D) before exercise (baseline) and 2-d post (48 hours), 4-d post (96 hours) and 7-d post (168 hours) after the final exercise session. # $p = 0.004$ for time effect between 2-d post and 7-d post.

Repeated measures ANOVA revealed a significant intervention by time interaction for adiponectin ($p = 0.04$). Figure 8.5 shows the resistance training group experienced a 31% reduction in adiponectin concentration two days after the final exercise session before returning towards baseline, where as the flexibility group experienced a 29% increase two days after the final stretching session and then maintained that level while the aerobic training group essentially experienced no change at any time. The effect size suggested large changes between the resistance and control interventions (Cohen's $d = 1.81$) and aerobic and control interventions (Cohen's $d = 0.81$) two days after the final exercise session that remained large seven days after the final exercise session for the

change between resistance and control interventions (Cohen's d = 1.48) and the aerobic and control interventions (Cohen's d = 1.02). Interestingly, there was also a large change between the two exercise interventions (Cohen's d = 0.87) two days after the final exercise session, but only a small difference (Cohen's d = 0.33) seven days after the final exercise session.

Repeated measures ANOVA revealed no significant intervention by time interaction for leptin ($p = 0.63$), however a time effect was noted ($p = 0.007$). Pair-wise analysis identified a trend for a reduction ($p = 0.08$) from pre exercise to two days after the final exercise session and a significant increase ($p = 0.007$) between the values at two days after the final exercise session to seven days after the final exercise session (Figure 8.6). A small practical change was observed for leptin concentrations between the resistance and control interventions (Cohen's d = 0.25) and aerobic and control interventions (Cohen's d = 0.24) two days after the final exercise session, but no change seven days after the final session or at any time between the two exercise interventions.

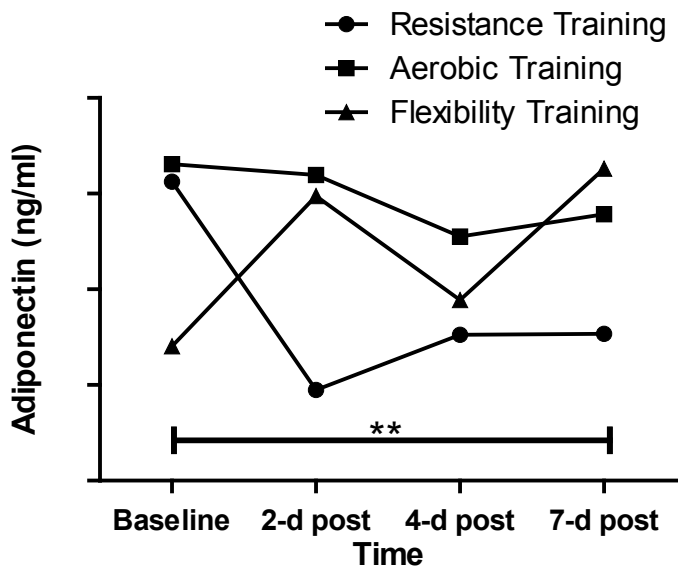

Figure 8.5: Adiponectin response to 8 weeks of exercise.
Mean values for adiponectin before exercise (baseline) and 2-d post (48 hours), 4-d post (96 hours) and 7-d post (168 hours) after the final exercise session. ** p = 0.04 for group by time interaction.

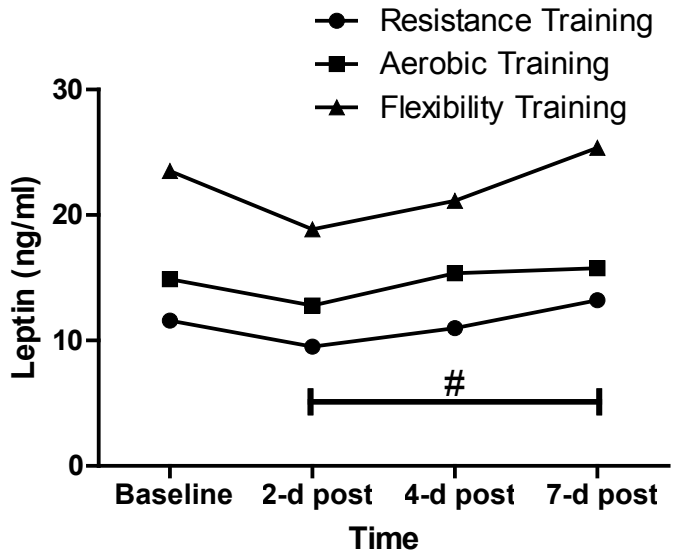

Figure 8.6: Leptin response to 8 weeks of exercise.
Mean values for leptin before exercise (baseline) and 2-d post (48 hours), 4-d post (96 hours) and 7-d post (168 hours) after the final exercise session. # p = 0.007 for time effect between 2-d post and 7-d post.

Several regression models were constructed to determine whether any variables of fitness (relative aerobic capacity, absolute upper body strength & absolute lower body strength) contributed to the change in glucose, adiponectin or leptin at different points during the

follow-up process at the end of the eight-week intervention period. Overall, fitness levels after the 8-week exercise intervention did not contribute to the change in glucose concentration at any time ($p > 0.05$). Post intervention fitness variables did contribute to the change in adiponectin ($p = 0.05$; $R^2 = 0.214$) and leptin ($p = 0.02$; $R^2 = 0.259$) at two days post exercise, however it did not contribute to the changes in adiponectin or leptin at any other time ($p > 0.05$). Stepwise regression identified the only contribution of the fitness variables to these changes was lower body strength for both adiponectin ($p = 0.005$; $R^2 = 0.206$) and leptin ($p = 0.012$; $R^2 = 0.171$). When the changes in fitness variables (post minus pre) over the eight-week duration were considered, again there was no overall contribution to the change in glucose ($p > 0.05$). In addition, there was no contribution to leptin ($p > 0.05$) at all follow-up times. The change in fitness made a significant contribution to the change in adiponectin at two days post ($p < 0.001$; $R^2 = 0.52$) and at seven days post ($p = 0.005$; $R^2 = 0.322$). Again, stepwise regression identified that only change in lower body strength was the major contributor to these changes in adiponectin at both two days ($p < 0.001$; $R^2 = 0.469$) and seven days ($p < 0.001$; $R^2 = 0.315$) post exercise. With the exception of the change in leptin from two days post to seven days post exercise ($p = 0.044$; $R^2 = 0.221$: stepwise lower body strength $p = 0.006$; $R^2 = 0.202$), there was no difference in the contributions when strength was considered relative to body mass (Table 8.2).

Additionally, the changes in body mass, BMI, and waist circumference were assessed to determine whether they contributed to the changes experienced in adiponectin and leptin concentrations. The change in anthropometric variables made a significant contribution to the change in adiponectin at two days post ($p = 0.009$; $R^2 = 0.302$), with stepwise regression identifying change in body mass was the only major contributor to this ($p =$

0.001; R^2 = 0.291). The change in anthropometrics did not contribute to the change in adiponectin at seven days post exercise (p = 0.547). The change in anthropometrics did however contribute to the change in leptin concentration at two days post exercise (p = 0.010; R^2 = 0.296) with stepwise regression indicating change in BMI (p = 0.009; R^2 0.186) along with change in BMI and body mass (p = 0.004; R^2 = 0.290) were the major contributors. While the change in anthropometrics contributed to the change in leptin concentrations at seven days post exercise (p = 0.014; R^2 = 0.280), no individual variable made a significant contribution to this change.

Table 8.2: Regression modelling analysis results

Regression model – Relative aerobic capacity, absolute lower body strength & absolute upper body strength

	Post intervention values					Intervention change values				
Dependent variable	**p value**	**R^2 value**	**Stepwise factor**	**p value**	**R^2 value**	**p value**	**R^2 value**	**Stepwise factor**	**p value**	**R^2 value**
Glucose pre - 2d change	0.633					0.951				
Glucose pre – 7d change	0.907					0.684				
Glucose 2d - 7d change	0.623					0.460				
Adiponectin pre - 2d change	0.050	0.214	Lower body strength	0.005	0.206	< 0.001	0.52	Lower body strength	< 0.001	0.469
Adiponectin pre - 7d change	0.148					0.005	0.322	Lower body strength	< 0.001	0.315
Adiponectin 2d – 7d change	0.761					0.814				
Leptin pre - 2d change	0.021	0.259	Lower body strength	0.012	0.171	0.725				
Leptin pre – 7d change	0.426					0.257				

Regression model – Relative aerobic capacity, relative lower body strength & relative upper body strength

	Post intervention values					Intervention change values				
Dependent variable	**p value**	**R^2 value**	**Stepwise factor**	**p value**	**R^2 value**	**p value**	**R^2 value**	**Stepwise factor**	**p value**	**R^2 value**
Glucose pre - 2d change	0.575					0.922				
Glucose pre – 7d change	0.898					0.349				
Glucose 2d - 7d change	0.613					0.274				
Adiponectin pre - 2d change	0.020	0.261	Lower body strength	0.002	0.252	< 0.001	0.457	Lower body strength	< 0.001	0.403
Adiponectin pre - 7d change	0.105					0.017	0.271	Lower body strength	< 0.001	0.264
Adiponectin 2d – 7d change	0.786					0.886				
Leptin pre - 2d change	0.010	0.296	Lower body strength	0.002	0.241	0.729				
Leptin pre – 7d change	0.257					0.303				
Leptin 2d - 7d change	0.044	0.221	Lower body strength	0.006	0.202	0.861				

8.5. Discussion

This study investigated the insulin sensitivity response to eight weeks of resistance training or aerobic training in comparison to a sham exercise control group (flexibility training). The major finding from this study was that eight weeks of exercise following the exercise guidelines [53, 55] three times a week in individuals with diet or oral hypoglycaemic medication treated T2D, did not significantly impact insulin sensitivity or insulin resistance estimated using HOMA2 equations. Additionally, glycaemic control was not changed with either exercise intervention and this was despite the exercising groups experiencing significant increases in strength and fitness. These findings however are in agreement with results reported following 12 weeks of resistance, aerobic or combined exercise completed three days a week [100], resistance training performed three times a week at home for six months [89] and also following 12 weeks of low intensity resistance training when insulin sensitivity was estimated using an insulin tolerance test [102]. Conversely, others have reported improved insulin sensitivity estimated using fasting indices [91, 92], oral glucose tolerance tests [80, 90] and when resistance exercise was combined with a high protein diet [193]. Additionally, insulin resistance has also been reduced by completing 12 months of aerobic exercise and aerobic combined with resistance exercise [166].

The fasting glucose response to eight weeks of exercise is interesting in itself by suggesting that both resistance and aerobic exercise have the ability to reduce fasting glucose to the same degree at two days following the final exercise session which then appears to be better maintained by resistance training in comparison to glucose levels increasing beyond baseline at seven days after the final aerobic exercise session as indicated by the large practical change in comparison to the control for the resistance

exercise intervention against no change compared to the control for the aerobic intervention. Although the difference in response between the two exercise groups was not statistically different, this particular trend suggests that perhaps eight weeks of exercise is not long enough for a statistical difference to be observed. This trend and previous findings of differences between resistance and aerobic training [93] highlight the need for more studies that compare the prescription of both forms of exercise to find the optimal dose and time-course for modifying glucose tolerance and insulin sensitivity. In addition, studies investigating the exercise prescription that follows the most recent exercise guidelines, which contains both aerobic and resistance training, in comparison to isolated aerobic or resistance exercise are warranted. Cumulative improvements in blood glucose levels have been observed over four weeks of combined exercise [122], which suggests that a longer study duration may have been required before differences between interventions would have been observed and indicates the need for different training frequencies to be investigated over extended durations.

A lack of change or an increase in insulin resistance has previously been theorised to be due to an increase in inflammatory profiles that results in a transient insulin resistance [159]. With this in mind, further research has been conducted to look at the metabolic profile of other markers of inflammation, such as adiponectin, an adipose derived cytokine that has been suggested to respond to exercise [33] and be an early marker of changes to insulin sensitivity [146]. The significant (and large practical) difference in the adiponectin response between the two exercise groups in this study potentially argues against this as although adiponectin decreased following resistance training, glucose levels were also reduced. This also highlights the potentially different mechanisms in which resistance and aerobic training alter blood glucose levels, as similar reductions in

fasting glucose were found despite different concentrations of adiponectin. Further, the identification that both absolute and relative lower body strength was the only independent fitness component contributing 21% to 52% of the change to adipocytokines from pre exercise to post exercise, supports such a hypothesis. Interestingly though, it appeared to be only the change from pre to post exercise and not the changes during the follow-up period from two days after the final session to seven days after the final session, that were contributed to by variables of fitness.

Following 12 months of high intensity aerobic exercise and combined aerobic and resistance exercise twice a week, concentrations of adiponectin were significantly increased while concentrations of leptin were significantly decreased [166]. This was reported along with reductions in high sensitivity C-reactive protein with the aerobic and combined exercise groups, where the combined group tended to continually decrease compared to the initial decrease that was maintained with aerobic exercise and significant reductions in the concentration of tumour necrosis factor-alpha (TNF-α) when compared to the non-exercising control group [166]. These findings were unable to be totally replicated, with adiponectin concentrations reducing following resistance exercise, being maintained with aerobic exercise and increasing in the sham exercise control –two days after the final training session. A trend for a reduction in leptin concentration was observed in all groups two days after the final session that then increased significantly back to or beyond baseline at seven days after the final session. Findings from Jorge et al. [100] differ again by reporting that after 12 weeks of either aerobic, resistance or combined exercise, adiponectin and TNF-α did not change and all groups (including the non-exercising control) experienced significant reductions in high sensitivity C-reactive protein. Interestingly though, expression of insulin receptor substrate-1, which is part of

the insulin signalling cascade, increased only after resistance exercise or when resistance exercise was combined with aerobic training [100]. Again signifying that different mechanistic pathways may be utilised in modulating insulin sensitivity and glycaemic control.

While the duration and intensity of training in this study is different to some of the previous studies, it has been able to replicate some data and provide a contrasting view to others. The main finding from this study is that while following the exercise guidelines for eight weeks, people with T2D experienced improved levels of cardio-respiratory fitness and muscle strength, however long-term glycaemic control (HbA1c) and insulin sensitivity were not affected at two, four or seven days after the final exercise session. It is likely that the short study duration of the intervention and low sample sizes affected the trend for the difference in fasting glucose response between the aerobic and resistance exercise groups and this justifies the need for further research into how each of the exercise modalities impact glucose tolerance over an extended duration, especially given reports that insulin receptor substrate-1 expression is increased with resistance exercise but not aerobic exercise [100]. Differences in the response to adiponectin concentration in this study further highlights the need for this area of research and particularly to clarify how adipose derived cytokines and markers of inflammation impact the clinical diabetes outcome of blood glucose levels. However, the low statistical power and lack of a direct measure of insulin sensitivity limits the generalisability of this study and must be considered in the interpretation of the findings.

8.6. Conclusion

From this study, it can be concluded that completing exercise in accordance with the guidelines for people with T2D for eight weeks is not sufficient for manipulating clinical diabetes outcomes of glycaemic control or insulin sensitivity, failing to prove the original hypothesis. What is clear however, is that exercise needs to be performed on an ongoing basis, as concentrations of glucose and leptin had deteriorated to a point above baseline values within seven days of completing the exercise intervention. While this does not clarify the optimal frequency at which exercise should be completed, it does highlight the acute nature of the response to a period of ongoing exercise training and the need to perform exercise on a regular basis. Whether the frequency and/or intensity of exercise participation to experience and maintain metabolic benefits changes over time, is still unknown.

Chapter 9

General Conclusions, Limitations/Delimitations, Recommendations

9. General Conclusions

The studies in this thesis set out to investigate the impact of a single session of resistance exercise on insulin sensitivity and glucose tolerance and then whether undertaking a period of ongoing training modifies this impact. This was done specifically in relation to exercise prescription guidelines for people with type 2 diabetes (T2D). With all of the data and research indicating that the prevalence of T2D is set to continue to increase [19, 20], the minimal effective exercise dose to achieve maximum adherence, for the primary prevention of T2D and the secondary prevention of diabetic complications and cardiovascular risk factors is required. Therefore this series of studies set out to explore the response of insulin sensitivity and glucose tolerance to resistance exercise and how long this response remained with the intention to better inform guidelines regarding training frequency.

The numerous diabetes prevention programmes around the world have shown the effectiveness of exercise interventions and healthy nutrition choices as part of a general improvement to an individual's lifestyle to reduce the incidence of T2D [163, 194-197], even in comparison to therapeutic medications [163]. These exercise interventions have mainly comprised aerobic type exercise though, which has been reflected in exercise guidelines for T2D. However, it seems clear that the exercise guidelines for individuals with T2D, especially in regards to resistance training, have been mainly based on data collected from individuals without T2D given that only two randomised controlled trials were cited in the initial population specific guidelines [55], and that only one randomised controlled trial involving resistance training in people with T2D [80] had been completed at the time the guideline was published. As the years progressed, more major health and diabetes organisations released exercise guidelines, yet even with the body of literature

surrounding resistance training in particular; there remains no consensus as to the most effective dose of resistance exercise for people with T2D.

Overall, from this series of studies the following conclusions were drawn:

i. A systematic review of the literature on resistance training interventions in people with T2D identified that diverse methods of measuring insulin sensitivity and glucose tolerance outcomes are commonly employed. Therefore only a general conclusion that a period of ongoing resistance training will result in an improvement to insulin sensitivity anywhere from 24 hours after the final exercise session through to 72-96 hours after the final exercise session was able to be drawn. Both of these time frames vary considerably from the recommendations of undertaking resistance training every two to three days [50-52, 71]. An important limitation identified from these studies was a lack of tracking the change to insulin sensitivity and glucose tolerance, therefore the length of time that insulin sensitivity was improved following a session, or a period, of resistance exercise is not known.

ii. Various investigators have used cytometric bead array analysis to measure multiple cytokines, adipokines and hormones in humans under a variety of conditions [137-139, 142]. While concerns around accuracy have seemingly been allayed [135], Timmons and colleagues [142] reported a lack of statistical agreement between values obtained through cytometric bead array analysis and the ELISA method. Therefore a preliminary methodological study was completed investigating the hypothesis that cytometric bead assay would be sensitive enough to accurately measure adipocytokines. In

agreement with Timmons and colleagues [142], statistical analysis of values obtained through both cytometric bead array and ELISA determined that hormone and adipocytokine concentrations were different, and that it was likely that the cytometric bead array was not sensitive enough to detect all of the required adipocytokines or accurate enough when they were detected, hence failing to prove our hypothesis correct.

iii. Oral glucose tolerance tests (OGTT) have been used to estimate insulin sensitivity and the change in insulin sensitivity following an exercise program in people with type 2 diabetes for many years [62, 63, 80, 90, 160], however repeatability of the OGTT has only been assessed between two and seven days after the initial test [150, 151], but never on two consecutive days. An investigation was undertaken into the hypothesis that an OGTT repeated on four consecutive days would produce similar estimates of insulin sensitivity. Analysis of the intra-individual variation of insulin sensitivity found a mean coefficient of variation of 7.8% and no statistical difference between days, allowing the conclusion that OGTTs provide replicable estimates of insulin sensitivity when repeated four days in a row in apparently healthy individuals, proving the hypothesis correct. However, the OGTT may not be suitable to estimate insulin sensitivity in those people with a metabolic disturbance such as T2D. This is an important finding as numerous studies have collected data on individuals with T2D following a single session of resistance exercise [62, 63] and ongoing resistance exercise [80, 90], using the OGTT. Therefore, caution is needed when interpreting this data.

iv. Findings regarding insulin sensitivity in response to a single session of resistance exercise in apparently healthy individuals are equivocal [64-68], although a time course study is yet to be completed. In a study investigating the insulin sensitivity response over four days to a single resistance exercise session, it was hypothesised that a single session of resistance exercise would not modulate insulin sensitivity in apparently healthy individuals. However, it was concluded that insulin sensitivity was impaired to a practically relevant level for at least four days in inactive apparently healthy individuals who were unaccustomed to resistance exercise, failing to prove the hypothesis. This however, concurred with findings from Howlett and colleagues who measured insulin sensitivity with a euglycaemic-hyperinsulinaemic clamp [66] and is likely due to an increase in levels of inflammation theorised to cause transient insulin resistance [159].

v. In contrast, in individuals with type 2 diabetes, a single session of resistance exercise appears to improve insulin sensitivity for up to 24 hours [62, 63], however each of these studies used OGTTs to estimate insulin sensitivity. With these and earlier findings from this thesis, it was hypothesised that a single session of resistance exercise would improve insulin sensitivity in people with type 2 diabetes when compared to apparently healthy individuals. In this case, estimates of insulin sensitivity were obtained using an index (HOMA2) from fasting glucose and insulin concentrations and identified no significant change to insulin sensitivity at 24 hours, 48 hours or 72 hours after a single session of resistance exercise, with no difference in the response in people with and without T2D, rejecting the hypothesis. This finding may be

different to previous findings using a similar exercise protocol in a similar population [62, 63] due to a different method of estimating insulin sensitivity being employed. This also provided information that resistance exercise following the broad exercise guidelines of 2-3 sets of 10 repetitions at a moderate-high intensity did not have a negative influence on metabolic health as theorised markers of transient insulin resistance [159] also did not change. However, given the reliance on fasting glucose and insulin concentrations that can only be obtained once a day, it was unclear whether any affect was so acute that it was being missed.

vi. Technological improvements in continuous glucose monitoring devices have been utilised to improve treatment of individuals' with type 1 diabetes [198] and others have recently reported the glucose response to a single session of exercise in individuals with type 2 diabetes to improve by decreasing [177, 181]. Using continuous glucose monitors to assess glucose control to compare resistance and aerobic exercise of a volume and intensity prescribed according to the exercise guidelines, it was hypothesised that a single session of resistance exercise would improve glucose control to a similar extent as that experienced following a single session of aerobic exercise. The findings were in opposition to those from other investigators [177, 181] and indicated the glucose response to a single, session of unaccustomed exercise in normally inactive individuals with type 2 diabetes had a negative, short-term impact on 24-hour glucose response and that this was independent of exercise mode. The key differences between the population of this study and other published

studies is the intensity of exercise had not followed the exercise guidelines previously and was much lower [177, 181] than that prescribed in this study.

vii. Metabolic health (explained through estimates of insulin sensitivity and measures of glucose control) has been reported to improve [62-64, 177, 181], or not [61, 65-68], depending on the population and the exercise dose. The initial studies from this PhD thesis using different populations (apparently healthy individuals, people with type 2 diabetes either taking no medication or oral hypoglycaemic medications, and people with insulin requiring type 2 diabetes) and different methods of estimating and measuring metabolic health using the same (or extremely similar) exercise dose, indicate metabolic health is impaired for a short period of time following such unaccustomed exercise. However, this does not appear to be due to transient insulin resistance associated with increased inflammation thought to accompany muscle damage [159] as adipocytokine markers of inflammation did not change. This highlights potential inadequacies of the methods for estimating insulin sensitivity and / or the intensity and volume of the recommended exercise prescription.

viii. The general consensus from chronic resistance training interventions is that insulin sensitivity and glycaemic control are improved [70, 72, 74, 75, 78, 165] however, the follow up period of each trial investigating these outcomes varied from 36-48 hours [79] to 72-96 hours after the final exercise session [90]. The hypothesis that compared to a sham exercise (flexibility training) control group; there would be no difference in the change to insulin sensitivity after aerobic or resistance exercise training was investigated using an eight

week intervention, exercising three days each week, prescribed according to the exercise guidelines. The results rejected the hypothesis and refuted findings reported previously [80, 90-92, 94] by finding that moderate to high intensity exercise was not sufficient to impact insulin sensitivity. However, while not being statistically significant, a moderate reduction in fasting glucose levels were observed two days after the final exercise session that appeared to be maintained for seven days after resistance training compared to reverting to baseline levels four days after the final session and deteriorating above baseline, seven days after the final exercise session in those undertaking aerobic exercise. Due to the follow-up period that was employed, this is a finding that has not been reported previously; although Cauza et al. [92] have reported that resistance training significantly reduces insulin resistance when compared to aerobic exercise in a small, RCT from which the results are limited by the lack of a non-exercise control group. While no solid conclusions can yet be drawn from this study, further investigation is warranted, as it would appear that resistance exercise may need to be undertaken less frequently than aerobic training to have the same glucose lowering effect. This however, might have important consequences of reducing the risk of renal disease, neuropathy, retinopathy and cardiovascular disease [4]. If this is proven to be the case, the positive implication for the prescription of exercise is increased adherence to exercise by individuals with T2D who may be more likely to complete exercise once or twice a week, compared to three, four or five days a week, given the common perception of not having enough time to exercise [157].

9.1. Limitations and Delimitations

Limitations and Delimitations of these studies include:

i. Only two of the studies completed utilised randomised designs; however the preliminary methodological studies and the initial resistance exercise response study investigated only a single group of participants to initially confirm methods to be used in the later studies, and the other resistance exercise response study compared two distinct populations (apparently healthy vs T2D) meaning that randomised designs were not appropriate.

ii. Participants were not recruited equally amongst genders, with the exception of the final acute resistance exercise study that investigated only males. However, all participant characteristics were extensively detailed allowing for the generalisation to other individuals with similar characteristics, additionally there is no clear evidence in the literature that suggests genders respond differently to exercise.

iii. The gold standard measurement for insulin sensitivity of the euglycaemic-hyperinsulinaemic clamp has not been used throughout this thesis. However, estimates from oral glucose tolerance tests and fasting indices correlate highly with the gold standard technique. Indeed, all of these methods only provide isolated ‘snapshots’ about glucose and therefore the final time course study of a single session of exercise was conducted using continuous glucose monitors.

iv. The durations of these investigations were short, investigating a single session of exercise and then eight weeks of exercising three days a week. The short nature of the eight week intervention did not allow for the assessment of the long-term adherence to the exercise program. However, assessing adherence was not the objective of this thesis but rather investigating the duration of any changes to resistance exercise to better inform, and provide guidance for training frequency.

v. The attention given to each group was identical over each of the acute interventions and the eight-week intervention by using a sham exercise group to counteract differences in researcher time given to the control group. Therefore, adherence or non-adherence to the intervention was not the result of increased or decreased opportunity to access external motivation and support.

vi. The follow-up of interventions investigating the time-course of change in response to exercise addresses limitations of previous interventions, and one study specifically used a technique that allowed for measurement continuously for 24 hours a day for a period of three days after the completion of the exercise session.

9.2. Recommendations

At the conclusion of these studies, several directions for future research are recommended:

i. Further investigations are required to determine (i) whether a similar glucose response occurs after single and multiple exercise sessions, and (ii) whether the glucose response is similar in individuals who are well trained in comparison to those who are inactive. This will help elucidate the frequency, intensity and timing of exercise prescription necessary in relation to initial and ongoing adaptations.

ii. Initial research using low intensity exercise interventions have shown beneficial results following a single session [177, 181] and following four to six weeks of resistance exercise [107] in people with type 2 diabetes. This also has potential implications for exercise compliance as exercise interventions that are simple and convenient to complete are more likely to be complied with long-term than interventions that require large time investments, special equipment and organisation in terms of having appropriate clothing and amenities. Therefore, further research using continuous glucose monitors during low intensity resistance exercise in people with type 2 diabetes is warranted.

iii. Therefore, finally, research should be completed with varied intensities of resistance exercise over extended durations to determine the intensity that

leads to the best compliance so that it can then be determined how best to implement exercise at that particular intensity. There is unequivocal evidence that exercise is the most powerful intervention to prevent and treat chronic disease such as type 2 diabetes, however ensuring people adhere to such interventions is the next challenge.

In Summary, from this series of studies, it is possible to suggest that a single session of resistance exercise following the broad exercise guidelines currently available for people with type 2 diabetes, has either no impact, or a short-term impairment on insulin sensitivity and glucose control in both apparently healthy individuals and those with type 2 diabetes. Interestingly this appears to be in contrast to data reported following exercise completed at a low intensity following a single exercise session or high intensity exercise after a period of chronic training. Without being able to accurately define the frequency of resistance training required to first improve and then maintain insulin sensitivity and glucose control, this dissertation has provided valuable information from which further studies can be designed to identify the minimum effective exercise prescription in people with type 2 diabetes. What can be concluded though is that for resistance exercise to be effective, it needs to be completed on a regular basis. The studies in this thesis have investigated resistance exercise prescribed in accordance with the current broad exercise guidelines and shown minimal effect on insulin sensitivity and other markers of metabolic health. Therefore, further research should be conducted using intensities different to those currently recommended, such as low intensity resistance training, to elucidate optimal gylcaemic control for both novice and trained people with type 2 diabetes.

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Appendix A

Peer Reviewed Journal Articles

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Review

Resistance training improves metabolic health in type 2 diabetes: A systematic review

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ARTICLE INFO

Article history:
Received 27 June 2008
Received in revised form
8 November 2008
Accepted 17 November 2008

Keywords:
Type 2 diabetes
Resistance training
Glycemic control
Insulin sensitivity
Systematic review

ABSTRACT

This paper systematically reviews the effect of resistance training (RT) on glycemic control and insulin sensitivity in adults with type 2 diabetes.

Twenty studies were included, with the volume, frequency and intensity of RT varying markedly. Supervised RT improved glycemic control and insulin sensitivity, however, when supervision was removed compliance and glycemic control decreased. Evidence indicates the mechanisms behind the improvements to glucose tolerance require further elucidation.

Although research demonstrates apparent benefits of RT for individuals with diabetes, further research is required to elucidate the minimum effective dose by describing frequency, intensity and the duration of acute and chronic improvements.

Contents

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Abbreviations: RT, resistance training; AT, aerobic training; CT, aerobic plus resistance training (combined training); RCT, randomized controlled trial; 1RM, one repetition maximum; 3RM, three repetitions maximum; HbA1c, glycosylated haemoglobin; OGTT, oral glucose tolerance test; AUC, area under the curve; FBG, fasting blood glucose; HOMA, homeostasis model assessment; ACSM, American College of Sports Medicine; ADA, American Diabetes Association; WHO, World Health Organization; GLUT4, glucose transporter 4; kcal/wk, kilocalories per week; LBM, lean body mass; GDR, glucose disposal rate.

0168-8227/$ – see front matter
doi:10.1016/j.diabres.2008.11.024

1. Introduction

The world-wide incidence of type 2 diabetes continues to increase [1] however, despite exercise being promoted as a vital part of the treatment process, exercise prescription does not vary between prevention and treatment. For individuals with existing diabetes, specific benefits of exercise include increased insulin sensitivity, improved glycemic control [2,3], improved lipid profile and lower blood pressure [3]. Importantly, individuals with diabetes completing exercise training using various exercise modes for between 8 weeks and 12 months have experienced decreased HbA1c by clinically significant levels (0.6%), improved insulin sensitivity and reduced serum triglycerides [4].

The American College of Sports Medicine (ACSM) endorses exercise as a treatment method for people with type 2 diabetes and currently recommends expending a minimum cumulative total of 1000 kcal/wk of energy from aerobic activities [5]. The American Diabetes Association (ADA) has similar recommendations for at least 150 min per week of moderate intensity aerobic physical activity and/or 90 min per week of vigorous aerobic exercise [6]. Accordingly, aerobic exercise has been the major focus for exercise-training studies due to consistent findings of improved glucose control [7,8], however long-term compliance to these recommendations remains low [9] necessitating the investigation of an effective strategy to improve adherence rates.

More recently, resistance training has been the focus of increased research and is suggested to improve glycemic control and insulin sensitivity partially via similar mechanistic pathways to aerobic training [10], and partially through discrete pathways providing additive insulin signalling benefits. The focus on resistance training is in part due to a recognition that individuals with type 2 diabetes, who are also likely to be obese or suffering from other co-morbidities, are likely to struggle to achieve the volume and intensity of aerobic training that is required to be effective [10,11], and therefore compliance to resistance training may be higher. Both the ACSM and the ADA have now included resistance training in their exercise prescription guidelines for younger individuals with type 2 diabetes and for older individuals with type 2 diabetes free of contraindications. The recommendations are; one set of 10–15 repetitions for 8–10 exercises twice a week [5] and, progressing to three sets of 8–10 repetitions three times a week [6]. These recommendations have largely been based on information regarding healthy individuals and the few [12–15] randomized controlled trials of resistance training in individuals with type 2 diabetes completed at the time that they were published. However, it should be noted that significant improvements to insulin sensitivity in healthy individuals have been reported only when resistance training was performed three or more days a week [16] and the responses of individuals with diabetes may differ. It is therefore the purpose of this paper to systematically review the literature on the effects of resistance training on the diabetes markers of glycemic control and insulin sensitivity in individuals with type 2 diabetes.

2. Methods

2.1. Search strategy

Ovid MEDLINE (1950 to August week 3, 2008), Ovid MEDLINE In-Process (September 02, 2008), OLD MEDLINE (1950–1965), CINAHL (1982 to August week 5, 2008) and EMBASE (1980 to 2008 week 35) electronic databases were searched on September 03, 2008. First, three keyword and categorical searches were performed (i) 'diabetes', or 'diabetes mellitus', or 'type 2 diabetes mellitus'; (ii) 'weight lifting', or 'resistance training', or 'strength training', or 'weight training', or 'progressive resistance training', or 'circuit training'; (iii) 'glucose intolerance', or 'blood glucose', or 'glucose', or 'glucose metabolism disorders', or 'glucose tolerance test', or 'insulin', or 'insulin resistance', or 'diabetes complications', or 'haemoglobin A', or 'glycosylated haemoglobin A', or 'HbA1c'. Second, categories i–iii were combined using 'and', limited to humans and reported in the English language with duplicates removed. In addition, reference lists of all publications meeting the inclusion criteria were manually searched to identify any relevant studies not found through electronic searching.

2.2. Inclusion and exclusion criteria

Studies that met the following criteria were included in this review: (i) published in English (ii) cohorts were adults above the age of 18 years with type 2 diabetes, (iii) a form of resistance training was included as an isolated intervention arm, (iv) it was an intervention study, (v) one diabetes marker (HbA1c, fasting glucose or insulin, insulin sensitivity) or an insulin signalling outcome were reported. Non-trial studies, review or opinion/editorial papers were excluded along with studies that did not report diabetes or insulin signalling markers or studies that investigated only individuals without diabetes. Interventions that combined resistance training with another intervention (aerobic training or diet) or did not involve ongoing training were also excluded.

2.3. Statistical analyses

To avoid misrepresentation of the presented data, a meta-analysis has not been conducted due to the methodological differences in terms of frequency and intensity of training, along with the number and type of exercises completed. Clinical significance has been interpreted as a 0.6% improvement in HbA1c [4]. Effect sizes were not calculated as only four papers included in the review provided enough information to enable effect size to be calculated.

3. Results

3.1. Search results

Twenty-four papers from 20 studies met the criteria and are included in this review. Search results are shown in Fig. 1. One doctoral dissertation was excluded, but its related publication identified and also excluded [17]. A paper reporting insulin sensitivity data was excluded [18] as this data had been

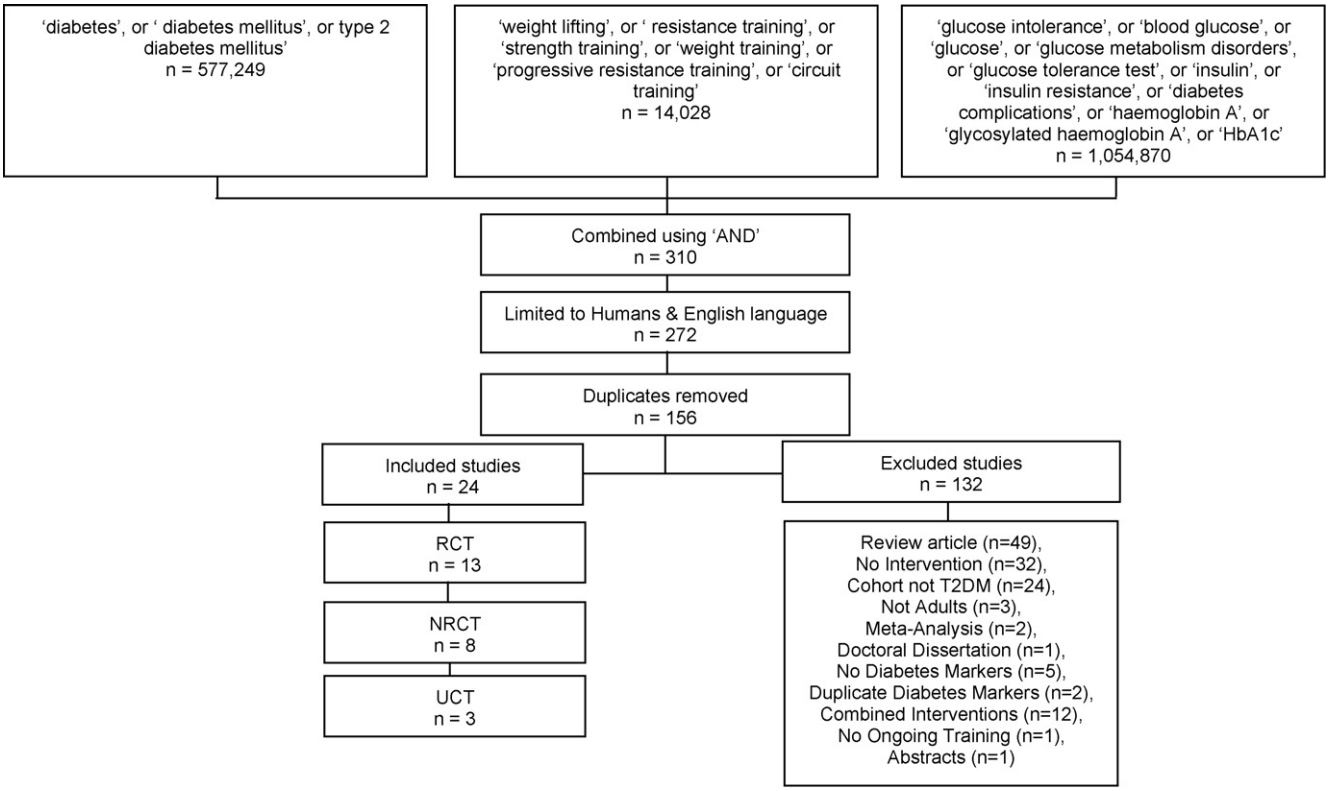

Fig. 1 – Sequence of searching and search results. RCT, randomized controlled trial; NRCT, non-randomized controlled trial; UCT, uncontrolled trial; combined interventions, aerobic and resistance training OR diet and resistance training.

Table 1 – Study quality.

Reference		Design					Subjects			Intervention			Compliance			Outcome Measures				
	Publication Date	Study Design	Randomization	Concealment	Assessor Blinding	Participant Blinding	Eligibility Criteria	Analysis between groups at baseline	Treatment vs Control similar at baseline	Details of RT exercise prescription	Intensity of RT	Adverse Events Reported	Loss to Follow-up	Attendance	Treatment of missing data specified	Statistical Analysis Specified	Primary &Secondary Outcomes Identified	Sample Size (determined by power calculations	Control &Treatment Method &Analysis the same	CV's Provided
Resistance Training																				
Winnick[28]	2008	RCT	Y	N	N	N	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N	Y	N
Baum [21]	2007	RCT	Y	N	N	N	Y	N	?	Y	Y	N	N	N	N	Y	N	N	Y	N
Brooks [22]	2007	RCT	Y	N	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y
Sigal [27]	2007	RCT	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N
Castaneda [29]	2006	RCT	Y	N	Y	N	N	Y	Y	Y	Y	N	N	N	N	Y	Y	N	Y	Y
Dunstan [25]	2006	RCT	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N
Gordon [26]	2006	RCT	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	Y
Cauza [24]	2005	RCT	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N
Cauza [23]	2005	RCT	Y	N	N	N	Y	Y	N	Y	Y	Y	N	N	N	Y	Y	N	Y	N
Dunstan [20]	2005	RCT	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y
Baldi [12]	2003	RCT	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y
Castaneda [13]	2002	RCT	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Dunstan [15]	1998	RCT	Y	N	N	N	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y
Ibanez [35]	2008	NRCT	N	N	N	N	Y	Y	N	Y	Y	N	N	Y	N	Y	Y	N	Y	Y
Colberg [31]	2006	NRCT	N	N	N	N	Y	Y	N	Y	Y	N	N	N	N	Y	Y	N	Y	N
Wojtaszewski [34]	2005	NRCT	N	N	N	N	N	Y	N	Y	Y	N	N	N	Y	N	N	N	Y	N
Fenicchia [32]	2004	NRCT	N	N	N	N	Y	Y	N	Y	Y	N	N	N	N	Y	Y	N	Y	N
Holten [19]	2004	NRCT	N	N	N	N	N	Y	N	Y	Y	N	N	N	N	Y	Y	N	Y	N
Ishii [30]	1998	NRCT	N	N	N	N	N	Y	Y	Y	Y	N	N	N	N	Y	Y	N	Y	N
Honkola [36]	1997	NRCT	N	N	N	N	N	N	?	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Smutok [37]	1994	NRCT	N	N	N	N	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	N	Y	N
Misra [40]	2008	UCT	N	N/A	N	N	Y	N/A	N/A	Y	Y	N	N	Y	N	Y	Y	N	N/A	N
Ibanez [39]	2005	UCT	N	N/A	N	N	Y	N/A	N/A	Y	Y	Y	Y	Y	N	Y	Y	N	N/A	Y
Eriksson [38]	1997	UCT	N	N/A	N	N	N	N/A	N/A	Y	Y	Y	N	N	N	Y	Y	N	N/A	N

RCT, Randomized controlled trial; NRCT, non-randomized controlled trial; UCT, uncontrolled trial; ?, not specified; Y, yes; N, no; N/A, not applicable; Adverse events reported, refers to whether the authors reported on adverse events, not that adverse events occurred; CV's provided, coefficient of variation of the measure reported within the methodology section, indicating reliability of the measure.

published previously [19]. A paper reporting phase one of a study [14] was excluded due to having a weight loss diet added to the resistance training, however a paper describing phase two [20] was included as dietary modification was ceased at the completion of phase one.

3.2. *Study design/quality assessment*

Most (10/13) of the papers based on randomized controlled trials (RCT) [13,15,21–28] reported eligibility criteria (Table 1); as did just more than half (6/11) of the trials that had no randomization.

Assessors were reported to be blinded in only three papers [13,27,29]. In all studies, previous medical intervention was maintained with changes to drug regimes occurring only where medically required. With one exception [30], all studies were completed using an out-patient design with participants under free-living conditions.

3.3. *Baseline characteristics*

Generally, there were no differences between intervention and control groups except where studies were intentionally designed to compare different cohorts [19,31–35] (Table 1). Baseline characteristics differed in one RCT [23] with the RT group having higher fasting blood glucose levels and lower body mass index and fat mass than untrained controls. Two studies did not report any analysis between groups at baseline [21,36], although there appears to be some differences in the data presented in these [21,36].

3.4. *Statistical analysis and power calculations*

The purpose of the research was outlined in all studies except two [21,24], however one paper [34] did not report the purpose despite a previous paper [19] from the same study reporting this information. Additionally, few papers (6/21) reported how missing data were treated (Table 1). With the exception of one study [36], the intervention and control groups were subjected to the same research methodology and analysis. Only one study [27] reported determining sample size by a priori power calculation.

4. Resistance training for type 2 diabetes

Within the included studies, RT was almost always completed using machines, including pin-loaded machines

Table 2 – Exercise intervention characteristics.

Author (year) country	N = Sample M/F Age y	Control/Comparison condition	Exercise mode and intervention	F: Frequency I: Intensity D: Duration	Strength test	Resistance training equipment	Duration	Supervision
Winnick et al. (2008) USA [28]	*n* = 59 Whites = 23 RT = 8 AT = 15 African = 36 RT = 12 AT = 24 M = ?/F = ? 25–60 y	White subjects Aerobic: 30–40 min walking on motorized treadmill, 3 week^{-1} for first 4 weeks expending ~600 kcal/wk, then 5 week^{-1} expending ~1000 kcal/wk	Progressive resistance training: 8 exercises: not specified, modified after 4 weeks in accordance with performance outcomes	F: NR I: NR D: NR	10RM All exercises	Machine weights	8 weeks	NR
Baum et al. (2007) Germany [21]	*n* = 40 RT = 13 Flex = 13 Vib = 14 M = 24/F = 16 62.9 ± 7.3 y	Flexibility: 8 exercises, 15 min Vibration: 8 exercises, 20 min	Resistance training 8 whole-body exercises: leg extension, seated leg flexion, leg press, seated calf raise, lat pulley, horizontal chest press, butterfly and rowing Wk 1–6 70% 1RM Wk 7–9 increase to 2 sets × 12 reps, Wk 10–12, 3 sets × 10 reps, 80% 1RM	F: 3 week^{-1} I: 1 set × 12 reps D: 45 min total	1RM Max isometric torque (quads)	Machine weights	12 weeks	All sessions: unspecified personnel
Brooks et al. (2007) USA [22]	*n* = 62 RT = 31 C = 31 M = 40/F = 22 66 ± 15.7 y	Standard type 2 DM care	Resistance training and standard care 5 whole-body exercises: upper back, chest press, leg press, knee extension and flexion Wk 1–8 60–80% 1RM Wk 10–14 70–80% 1RM	F: 3 week^{-1} I: 3 sets × 8 reps High intensity D: 45 min total, 5 min warm-up and cool down	1RM - Upper and lower body	Pneumatic Machine weights	16 weeks	NR
Sigal et al. (2007) Canada [27]	*n* = 251 RT = 64 AT = 60 CT = 64 C = 63 M = 160/F = 91 54.7 ± 7.5 y	Aerobic: 3 week^{-1} 45 min @ 75% HRmax Combined: Aerobic and resistance 3 week^{-1} Control: No exercise intervention	Resistance training 7 whole-body exercises: Abdominal crunches, seated row, biceps curls, bench press, leg press, shoulder press and leg extension. Progressing from 1 set of 15 reps @ 15RM to 3 sets of 8 reps @ 8RM	F: 3 week^{-1} I: 2–3 sets × 7–9 reps D: NR 2–3 min between sets	8RM	Machine weights	26 weeks	Weekly first 4 weeks, then fortnightly: Unspecified personnel

Table 2 (*Continued*)

Author (year) country	N = Sample M/F Age y	Control/Comparison condition	Exercise mode and intervention	F: Frequency I: Intensity D: Duration	Strength test	Resistance training equipment	Duration	Supervision
Castaneda et al. (2006) Germany [29]	*n* = 18 RT = 13 C = 5 M = 6/F = 12 66 ± 8 y	Standard type 2 DM care	Resistance training 5 whole-body progressive exercises: 2 upper body, 3 lower body exercises 60–65% 1RM, increasing to 75–80% 1RM by week 4	F: 3 week^{-1} I: 3 sets × 8 reps Moderate-high intensity D: 45 min total, 5 min warm-up and cool down	1RM - 2 upper and 3 lower body exercises	Pneumatic Machine weights	16 weeks	All sessions: unspecified personnel
Dunstan et al. (2006) Australia [25]	*n* = 60 Int = 28 C = 29 M = 33/F = 27 60.5 ± 8.2 y	Home-based resistance training: given 1 dumbbell and weight plates. Monthly telephone call	Community gym-based resistance training 8 whole-body exercises: similar to program undertaken in a supervised setting previously	F: 2 week^{-1} I: 3 sets × 8 reps Increase weight when able to perform 3 sets × 8 reps D: NR	1RM -Bench press - Leg extension	Machine and free weights	12 months	Yes, YMCA staff
Gordon et al. (2006) USA [26]	*n* = 30 RT = 15 C = 15 M = 15/F = 15 67 ± 11 y	Standard type 2 DM care: no exercise, fortnightly telephone interview	Resistance training and standard care 5 whole-body progressive exercises: knee extension, chest press, leg curl, upper back and leg press 60–65% 1RM, increasing to 75–80% 1RM by week 4	F: 3 week^{-1} I: 3 sets × 8 reps D: 45 min total, 1–2 min rest between sets, 5 min warm-up	1RM	Pneumatic Machine weights	16 weeks	Yes: unspecified personnel
Cauza et al. (2005) Austria [24]	*n* = 43 RT = 22 AT = 17 M = 22/F = 21 56 ± 6.6 y	Aerobic training: cycle 3 week^{-1}, 15 min progressing 5 min per week to 90 min @ 60% VO_{2max}	Resistance training 10 min warm-up moderate cycling Minimal weight wk 1 and 2 to teach technique Progressive resistance from wk 3 10 whole-body exercises: bench press, chest cross, shoulder press, pull downs, biceps curls, triceps extensions, situps, leg press, calf raises, leg extensions, increasing to 4, 5 and 6 sets/wk	F: 3 week^{-1} I: 3 sets/wk × 10–15 reps i.e. 1 set × 10–15 reps each session Weight increase when able to complete 15 reps D: NR	1RM - bench press - rowing - leg press All seated	Machine and free weights	4 months	All sessions: Professional instructor, Physician

Cauza et al. (2005) Austria [23]	$n = 15$ RT = 8 AT = 7 M = 4/F = 11 55 ± 7.8 y	Aerobic training: cycle 3 week^{-1}, 15 min progressing 5 min per week to 90 min @ 60% VO_{2max}	Resistance training 10 min warm-up moderate cycling Minimal weight wk 1 and 2 to teach technique Progressive resistance from wk 3 10 whole-body exercises: bench press, chest cross, shoulder press, pull downs, biceps curls, triceps extensions, sit-ups, leg press, calf raises, leg extensions, increasing to 4, 5 and 6 sets	F: 3 week^{-1} I: 3 sets × 10–15 reps Weight increase when able to complete 15 reps D: NR	1RM - seated bench press	Machine and free weights	4 months	All sessions: Professional instructor, Physician
Dunstan et al. (2005) Australia [20]	$n = 36$ RT = 14 C = 12 M = 21/F = 15 60–80 y	Home-based flexibility training, 3 week^{-1}, telephoned fortnightly	Home-based resistance training 9 whole-body exercises: lying dumbbell flies, seated single-leg extension, dumbbell shoulder press, dumbbell bent-over row, standing leg curl, dumbbell biceps curls, dumbbell triceps kickback, abdominal curls. 60–80% 1RM Additional weights provided to facilitate progression	F: 3 week^{-1} I: 3 sets × 8–10 reps D: NR	1RM	Free weights	6 months	No, telephone monitoring weekly first 4 weeks, then fortnightly
Baldi and Snowling (2003) New Zealand [12]	$n = 18$ RT = 9 Con = 9 M = 18/F = 0 47.9 y	No exercise completed	Resistance training 10 whole-body progressive exercises: not specified 1 set × 12 reps in wk 1 then 2 sets × 12 reps. Resistance progressed by 5% when able to successfully complete the program	F: 3 week^{-1} I: 2 sets × 12 reps Max weight for 10 reps for upper body and 15 reps for lower body exercises Moderate intensity D: NR, 60 s rest between sets	Max isokinetic torque - Leg and arm flexion	NR	10 weeks	All sessions: Unspecified personnel
Castaneda et al. (2002) USA [13]	$n = 62$ RT = 31 C = 31 M = 22/F = 40 66 ± 11.8 y	Standard type 2 DM care: Telephone call fortnightly	Resistance training 5 whole-body progressive exercises: chest press, leg press, upper back, knee extension and flexion. Wk 1–8 = 60–80% 1RM Wk 10–14 = 70–80% 1RM Wk 9 and 15 = 10% decrease	F: 3 week^{-1} I: 3 sets × 8 reps High intensity D: 45 min total, 5 min warm-up and cool down	1RM - 2 upper and 3 lower body exercises	Pneumatic Machine weights	16 weeks	All sessions: Unspecified personnel

Table 2 (*Continued*)

Author (year) country	*N* = Sample M/F Age y	Control/Comparison condition	Exercise mode and intervention	F: Frequency I: Intensity D: Duration	Strength test	Resistance training equipment	Duration	Supervision
Dunstan et al. (1998) Australia [15]	*n* = 27 RT = 15 C = 12 M = 17/F = 10 50 ± 10.4 y	Control: no exercise intervention with medical review fortnightly	Progressive circuit resistance training 10 whole-body exercises: leg extension, bench press, leg curl, biceps curls, behind neck pull down, calf raise, overhead press, seated rowing, triceps extension and abdominal curls. Wk 1–2 = 2 sets Wk 3–8 = 3 sets	F: 3 week^{-1} I: 2–3 sets × 10–15 reps D: 60 min total, 30 s per exercise, 30 s active rest including warm-up and cool down	1RM - all intervention exercises performed	Machine and free weights	8 weeks	All sessions: Instructor, Physician

RT, resistance training; Flex, flexibility training; Vib, vibration training; 1RM, 1 repetition maximum; mins, minutes; Max, maximum; C, control; standard type 2 DM care, routine medical care for type 2 diabetes mellitus; NR, not reported; AT, aerobic training; CT, combined aerobic and resistance training; Int, intervention; HRmax, maximum heart rate; wk, week; secs, seconds; VO_{2max}, maximal oxygen uptake.

(20/24 papers), with some studies incorporating the use of free-weights [15,23–25,30,32,37] (Table 2). Two studies varied the delivery of RT using circuit-type training [15,36]. A whole-body training protocol, mostly progressive in nature where the weight lifted, or sets and repetitions completed increased at varying stages was favoured by most researchers (19/20 studies; Table 2). However, one study [19,34] used only three exercises and focused solely on the lower limbs.

4.1. *Frequency*

Resistance training protocols were commonly performed on three non-consecutive days/wk (Table 2), although one non-randomized study [30] admitted their participants to hospital to complete low intensity RT 5 days/wk. Four studies [25,36,38,39] performed RT on 2 days/wk, with one study [25] prescribing 2 days/wk to maintain benefits achieved from previously training 2 days/wk.

4.2. *Intensity*

The intensity of each RT protocol varied considerably, with some studies giving precise information about initial intensities and progression points, while other studies provided vague details of increasing the weight (by an unspecified amount) when participants were able to complete a certain number of sets and repetitions (Table 2). Two studies [35,39] specifically reported completing power exercises using low weight and high velocity movement, in addition to their normal RT program. Two studies prescribed the training weight as percentage 1RM but measured strength using 3RM [19,34] or KIN-COM [30], while another study [33] prescribed RT based on percentage 10RM after conducting 1RM testing. The precise intensities reported for each RCT are shown in Table 2.

4.3. *Duration*

The duration of all studies varied from 4–6 weeks to 12 months of training. One study [32] reported the acute effects of RT, before also reporting 6-week follow-up data. An additional study reported data at 6 weeks [19,34], while another study reported a duration of 4–6 weeks [30]. Six studies had durations of 6–16 weeks [12,15,28,31,35,40], and another study examined changes over 6 months [27]. Additionally, one paper reported a 6-month follow-up period [20] after a 6-month RT and weight loss intervention [14]. One study reported a 2-month supervised introductory phase, followed by 12 months of home-based maintenance [25].

4.4. *Compliance*

When the interventions were completed at a specific exercise venue, eight papers reported compliance levels of ≥85% with most of the training completed under supervision (Table 2). When direct supervision was removed during maintenance programs at home or at a leisure-centre, adherence dropped to 67–72% [20,25] and 68% [25], respectively.

4.5. *Adverse events*

Although information regarding adverse events was not reported in 6 of 13 papers reporting RCT's [15,21,22,26,28,29] and only 3 of 11 papers describing non-RCT's reported information on adverse events [36,38,39] (Table 1), the interventions seemed to be well tolerated in these clinical populations with co-morbidities. Cases of hypoglycemia were reported in five RT studies, during training [25], immediately following training [13], during the night after RT [23], or at unspecified times, with medication decreased to counteract this outcome [27,38]. Hypoglycemic events were also reported with combined training (CT), AT and in the control group, with medication adjusted for this [27]. Additionally, hypoglycemia occurred frequently in one individual both before and after AT [23], while seven hypoglycemic events were reported in a control group [13]. In only one case, was hypoglycemia severe enough to warrant medical attention [25]. One study reported musculoskeletal conditions requiring the program to be modified [27], episodes of chest pain were reported twice [13,27] and one study reported a case of hypotension [38].

5. Glycemic control

5.1. *Glycosylated haemoglobin*

Glycosylated haemoglobin (HbA1c) is considered the optimal way of measuring long-term (120 days) glycemic control [41], with HbA1c values of <7.0% accepted as representing good glucose control [41]. Nine RCT's reported HbA1c data (Table 3), with two studies [13,22,24,26] reporting HbA1c reduced by 1.0–1.2%, from above 8.0% prior to 16 weeks of moderate-high intensity training. Baldi and Snowling [12] showed an improvement over the intervention period which approached significance ($P = 0.057$) after 10 weeks of RT with HbA1c levels reducing from 8.9% to 8.4%. Maintenance programs completed at home [20,25], or at a community-gym [25] reported glycemic control returned towards baseline after 6 months or became worse after 12 months, which is likely to be a result of decreased compliance to the prescribed training. Interestingly, RT appears to be as effective as AT at improving HbA1c when compared to control groups [27] and more effective when compared to AT [24]. This finding requires further validation though as the RT group appeared to spend a larger volume of time training than the AT group. Sigal et al. [27] however, concluded that CT was superior at improving glycemic control to either RT or AT on their own.

Seven non-RCT's reported HbA1c data with only the trials reporting different subjects (diabetes vs. non-diabetes) indicating significant differences. Two [38,40] reported an improvement over time, although another [30] reported a 2% improvement in HbA1c which was not significant.

The greatest improvements to glycemic control occurred when HbA1c was poor (>8.0%) at baseline however, based on current literature [4], clinically relevant improvements of 0.6% were generally seen with moderate-high intensity RT or where the duration of training lasted 10 weeks or longer. The exception to this was 4–6 weeks of low intensity RT 5 days/wk resulting in a 2.0% improvement of HbA1c [30], although this study was not randomized and participants were remarkably light and had a low body mass index, reducing the generalizability of this study.

5.2. *Fasting blood glucose*

Fasting blood glucose (FBG) is less frequently used as a measure of glycemic control but can be a substitute when HbA1c is not measured, for instance when the intervention duration is less than that required for a change in glycemic control to be fully reflected in HbA1c (<3 months). Seven RCT's reported FBG levels (Table 3), with only one [24] reporting a significant change when compared to the comparison group (AT). This was quite a large improvement (3.2 mmol/L) and included some subjects taking insulin, where no other study included subjects taking insulin. This study however was not identically matched in terms of volume, with the RT group completing up to six sets of 10–15 repetitions per week for 10 exercises (estimated to be 120 min of exercise per week plus 120 min of rest/recovery during the sessions) and the AT group completing up to 90 min per week. Again, only two [39,40] of six [19,31,32,38–40] non-RCT's reporting FBG indicated an improvement over time.

6. Insulin sensitivity

6.1. *Euglycemic–hyperinsulinemic clamp*

Although considered the gold-standard for determining insulin sensitivity levels [42], only two studies used the euglycemic–hyperinsulinemic clamp [19,30]. Holten et al. [19] reported that despite individuals with diabetes having significantly lower glucose disposal rates (GDRs) and therefore greater insulin resistance than controls, leg glucose clearance rates increased during the second stage of the euglycemic–hyperinsulinemic clamp, showing that improvements are achievable with RT despite being less sensitive to insulin. Ishii et al. [30] also used an euglycemic–hyperinsulinemic clamp, reporting a 48% ($P < 0.05$) increase in insulin sensitivity with RT and no change in sedentary individuals with diabetes acting as controls.

Comparing these studies is difficult due to one [19] reporting GDR at varying levels of insulin infusion, and another [30] reporting final GDR. However, it is likely that RT for 4–6 weeks will result in increased insulin sensitivity.

6.2. *Oral glucose tolerance test*

Insulin sensitivity using area under the curve (AUC) equations for glucose and insulin levels during an oral glucose tolerance test (OGTT) has been validated against the euglycemic–hyperinsulinemic clamp [42] with lower glucose values indicating better glucose tolerance and lower insulin values indicating increased insulin sensitivity. The OGTT was used in two RCT's [15,21] (Table 3), with results indicating an improvement in insulin sensitivity when compared to sedentary controls [15] but not when compared to vibration or flexibility training [21], although the method of performing this analysis varied from other studies as blood was drawn

Table 3 – Metabolic outcomes.

Author (year) country	Group	Time of follow-up	Type of change	HbA1c (%)	Glucose (mmol/L)	Insulin (pmol/L)	Insulin sensitivity method	Insulin sensitivity
Winnick et al. (2008) USA [28]	Whites RT AT African RT AT	NR	Pre:Post Δ Time effect Group × time	7.9 ± 2.0:NR 7.8 ± 1.2:NR 6.5 ± 1.0:NR 7.6 ± 1.5:NR NR NR			HOMA IR	6.8 ± 4.8:NR +13.2% 10.6 ± 8.5:NR −3.68% 5.8 ± 2.4:NR −19.15% 8.6 ± 7.4:NR +3.79% NR $P < 0.05$ RT African v Whites $P > 0.05$ AT African v Whites
Baum et al. (2007) Germany [21]	RT Vib Flex	72–96 h	Pre:Post Δ Time effect Group × time	6.8% ± 0.17:NR +0.2 ± 0.15 Δ 7.3% ± 0.66:NR −0.3 ± 0.22 Δ 6.7% ± 0.26:NR +0.34 ± 0.26 Δ NR NR	6.99 ± 1.28: 6.66 ± 1.22 7.38 ± 3.16: 6.77 ± 1.94 6.66 ± 1.39: 6.38 ± 1.22 NR NR		OGTT – ear lobe Glucose only	NR:NR −5.6% Δ NR:NR −6.3% Δ NR:NR 0.00% Δ $P < 0.05$ RT and Vib NR
Brooks et al. (2007) USA [22]	RT Con	72 h	Pre:Post Δ Time effect Group × time	8.7 ± 10.0: 7.6 ± 8.4 −1.0 ± 1.1 Δ 7.8 ± 8.9: 8.3 ± 7.2 +0.4 ± 1.7 Δ NR $P < 0.001$	8.8 ± 2.8:7.9 ± 2.2 −0.9 ± 2.8 Δ 9.9 ± 3.9:9.5 ± 3.3 −0.3 ± 4.5 Δ NR $P = 0.92$	116 (124):105 (70)* −16 (69)* Δ 115 (131):133 (126)* +6 (86)* Δ NR $P = 0.27$	HOMA-IR	7.1 (5.7):5.3 (5.5)* −0.7 (3.6)* Δ 6.7 (9.0):6.4 (6.8)* +0.8 (3.8)* Δ NR $P = 0.05$
Sigal et al. (2007) Canada [27]	RT AT CT Con	Minimum 48 h	Pre:Post Time effect Group × time	7.5 ± 1.5: 7.2 ± 1.5 7.4 ± 1.5: 7.0 ± 1.5 7.5 ± 1.5: 6.6 ± 1.6 7.4 ± 1.4: 7.5 ± 1.5 $P = 0.018$ RT $P = 0.002$ AT $P < 0.001$ CT $P = 0.57$ Con $P = 0.038$ RT v Con $P = 0.007$ AT v Con $P = 0.001$ CT v RT $P = 0.014$ CT v AT				

Dunstan et al. (2006) Australia [25]	Centre Home	48 h	Pre:Post Δ Time effect Group × time	7.8 ± 0.9:NR +0.1 ± 1.0 Δ 7.5 ± 0.5:NR +0.2 ± 1.2 Δ $P < 0.05$ both grps NS	9.0 ± 2.0:NR −0.3 ± 1.8 Δ 8.4 ± 1.9:NR −0.2 ± 2.2 Δ NS NS	143.7 ± 66.1:NR −21 ± 47.6 Δ 126.6 ± 55.1:NR −8.5 ± 32.8 Δ $P < 0.05$ centre NS	HOMA	46.9 ± 26.1:NR +9.4 ± 16.4 Δ 50.7 ± 24.6:NR +2.4 ± 12.4 Δ $P < 0.05$ centre NS
Gordon et al. (2006) USA [26]	RT Con	72 h	Pre:Post Time effect Group × time	8.7 ± 1.9:7.7 ± 1.6 8.0 ± 1.6:8.3 ± 1.6 NR $P < 0.01$		173 ± 108:132 ± 54 157 ± 101:168 ± 139 NR $P < 0.05$	HOMA-IR	8.5 (7.2):5.3 (6.3)* 6.7 (7.8):7.1 (7.4)* NR $P = 0.08$
Cauza et al. (2005) Austria [24]	RT AT		Pre:Post Δ Time effect Group × time	8.3 ± 8.0:7.1 ± 1.7 −1.2 Δ 7.7 ± 1.2:7.4 ± 1.2 −0.3Δ $P = 0.001$ RT, NS AT $P = 0.009$	11.32 ± 7.62:8.16 ± 3.77 −3.2 Δ 8.88 ± 2.06:8.83 ± 2.31 −0.05 Δ $P < 0.001$ RT, NS AT $P = 0.002$	130.9 ± 84.0:118.4 ± 85.4 −12.5 Δ 105.1 ± 77.5:125.6 ± 96.1 +20.46 Δ NS both grps $P = 0.04$	HOMA-IR	9.1 ± 7.0:7.2 ± 5.6 −2.0 Δ 6.8 ± 5.8:8.4 ± 7.8 +1.5 Δ $P = 0.04$ RT, NS AT $P = 0.009$
Cauza et al. (2005) Austria [23]	RT AT		Pre:Post Time effect Group × time	7.5 ± 1.4:7.0 ± 2.1 8.0 ± 3.8:7.6 ± 4.8 NS both groups NR				
Dunstan et al. (2005) Australia [20]	RT Con	48 h	Pre:post Δ Time effect Group × time	Returned towards baseline Returned towards baseline $P < 0.05$ NR	NR:NR +0.3 ± 2.2 Δ NR:NR −0.5 ± 2.1 Δ NS both grps NS	NR:NR −0.1 ± 46.8 Δ NR:NR −19.3 ± 50.1 Δ $P < 0.05$ Con, NS RT NS	HOMA-IR	NR:NR +0.04 ± 5.5 Δ NR:NR +5.4 ± 6.5 Δ $P < 0.05$ Con, NS RT NS
Baldi and Snowling (2003) New Zealand [12]	RT Con	36–48 h	Pre:Post Time effect Group × time	8.9 ± 3.6:8.4 ± 1.8 8.5 ± 2.4:8.4 ± 1.8 $P = 0.057$ RT, 0.64 Con NR	12.0 ± 2.7:11.4 ± 2.4 11.1 ± 3.3:11.0 ± 3.0 $P < 0.05$ RT NR	268.1 ± 35.4:146.5 ± 28.5 191.7 ± 63.9:214.6 ± 52.1 $P < 0.05$ RT NR	Insulin sensitivity index 0.120	20.3 ± 3.9:22.6 ± 3.9 22.2 ± 11.4:19.9 ± 5.1 NS NR
Castaneda et al. (2002) USA [13]	PRT Con	48 h	Pre:Post Δ Time effect Group × time	8.7 ± 1.7:7.6 ± 1.1 −12.6 ± 11.1% Δ 8.4 ± 1.7:8.3 ± 2.8 +1.2 ± 5.6% Δ NR $P = 0.01$	8.8 ± 2.8:7.9 ± 2.2 9.7 ± 3.9:8.9 ± 3.9 NR $P = 0.34$			
Dunstan et al. (1998) Australia [15]	CRT Con	48 h	Pre:Post Δ Time effect Group × time	8.2 ± 1.9:8.0 ± 1.9 8.1 ± 2.1:8.3 ± 2.4 NS both grps NS	9.6 ± 3.5:9.4 ± 3.1 9.9 ± 4.2:9.8 ± 4.5 NS both grps NS	64.3 ± 49.1:63.1 ± 48.8 82.6 ± 36.4:93.8 ± 43.7 NS both grps NS	OGTT - Glucose AUC - Insulin AUC	−22 ± 240Δ −2183 ± 6053Δ +191 ± 291Δ +3947 ± 5352Δ NR $P < 0.05$ glucose and insulin

RT, resistance training; Flex, flexibility training; Vib, vibration training; Con, control; NR, not reported; AT, aerobic training; NS, not significant; PRT, progressive resistance training; CRT, circuit resistance training; CT, combined aerobic and resistance training; *, values are median (interquartile range). Castaneda [29] did not report any metabolic variables.

from the ear lobe, rather than the commonly used antecubital vein and only glucose was measured, not insulin as well. Two non-RCT's [32,37] completed OGTT's with AUC for glucose and insulin improving over time with both RT and AT [37], although Fenicchia et al. [32] showed no change after 6 weeks of RT despite reporting an improvement 12–24 h after the first RT session, however, the time of completing the OGTT post training was later. The time utilized for each OGTT trial varied considerably between 24 and 72–96 h post-training (Table 3). This may be a factor in whether studies reported improvements or not as it is still unclear precisely how long insulin sensitivity remains increased following RT, and therefore acute rather than chronic training effects could have been reported. The training regimes may also have contributed to the varied results as different protocols at different intensities were employed by each study.

6.3. *Homeostasis model assessment*

The homeostasis model assessment (HOMA) is a mathematical model of determining insulin resistance from fasting glucose and insulin concentrations which has been validated against the euglycemic–hyperinsulinemic clamp [42]. This was the most common method of determining insulin resistance and estimating insulin sensitivity, possibly because of its ease and speed of completion as it requires only a fasting blood sample, with six papers describing five RCT's using this method [20,22,24–26,28] (Table 3). HOMA was originally developed in 1985 and updated in 1996 to estimate insulin sensitivity [43] although it is unclear whether any of the studies using HOMA modelling utilized the updated version.

A reduction in insulin resistance after 4 months of RT ($P = 0.04$) was reported in a study with 22 participants [24], while 12 months of centre-based maintenance following a 2-month introductory period saw insulin sensitivity improve ($P < 0.05$) [25]. Comparing RT with the control group significantly improved ($P < 0.05$) [22] and tended to improve ($P = 0.08$) [26] insulin resistance, while RT compared with AT also showed a trend towards ($P = 0.09$) improvement of insulin resistance [24]. Winnick et al. [28] reported a significant improvement in insulin resistance for African Americans completing RT when compared to Whites completing RT. However, there was no difference between ethnicity when AT was completed.

Insulin resistance improved by 3.2 when calculated using HOMA 72 h after the final session [26], which is supported by a 9.4% improvement in insulin sensitivity when measured 48 h after the final RT session [25]. Additionally one non-RCT [31] reported HOMA, stating no change in insulin resistance 48–72 h following the final RT session. The limited number of studies and the variation in HOMA limit the ability to make conclusions. However, insulin sensitivity seemed to at least tend to improve compared to a comparison group [15,22,24,26], though how long this improvement remains is unclear.

6.4. *Insulin sensitivity index*

The insulin sensitivity index is another validated mathematical model for determining insulin sensitivity [42], but was used by only one RCT [12] and one uncontrolled trial [39] with each using a different model. Contrasting results were reported, with Baldi and Snowling [12] finding no evidence of change in either RT (10 weeks) or control groups, while Ibanez et al. [39] observed a 46% improvement in insulin sensitivity ($P < 0.001$) after 16 weeks of RT. This difference could be time related as the improvement was measured 24 h after the final session [39] compared to 36–48 h when no improvement was seen [12], or this could be related to intensity or duration of training.

6.5. *Short insulin tolerance test*

One non-RCT [40] used the short insulin tolerance test to measure insulin sensitivity. This test was completed 72–96 h after the final training session of a 12-week program completed with free weights in a physiotherapy clinic, and reported a significant improvement in insulin sensitivity.

7. Insulin signalling

Only two studies reported data on glucose transport and insulin signalling in individuals with diabetes [19,29,34] with one of these being a RCT [29]. Improved glucose disposal, as measured by incorporation into muscle glycogen, support findings using the euglycemic–hyperinsulinemic clamp [19,29]. Changes in the glucose transporter-4 (GLUT4) are less clear with an earlier study [19] reporting a 40% increase ($P < 0.05$) in GLUT4 density compared to a more recent study [29] reporting no evidence of change in GLUT4 gene or protein expression. This could be due to population differences (males vs. females) or the different training protocols (whole-body vs. lower-limb).

Eight weeks of moderate-high intensity RT resulted in increased protein content of the insulin receptor, protein kinase-B, and glycogen synthase (GS) to similar levels in individuals with diabetes and healthy control subjects. However, no training effect was observed for protein content of insulin receptor substrate-1, the p85 subunit of phosphatidylinositol(PI)-3-kinase, or percent GS activity [19]. Moderate-intensity RT resulted in similar changes to various AMP-activated protein kinase (AMPK) subunit isoforms (α1: +16%, β2: +14%, γ1: +29%, γ3: −48%) in patients with diabetes and healthy controls [34], while muscle glycogen levels significantly increased with RT [19,29], when compared to controls ($P = 0.04$) [29].

8. Muscle strength

Ten papers from seven RCT's reported muscle strength data (Table 4), with all but one study [25] reporting improvements of at least 50% after completing RT. The study [25] reporting a decrease ($P < 0.05$) in strength after RT, reported small losses after 12 months of a home or leisure-centre based maintenance program following on from a 2-month supervised intervention period, although only lower body strength in the home-based group decreased below baseline, and was likely to be due to not being able to maintain the appropriate intensity. In most cases [13,20,22,29] these changes were significant when compared to sedentary controls, but not when

Table 4 – Body composition markers.

Author (year) country	Group	Type of change	Mass (kg)	BMI (kg m^{-2})	Waist circumference (cm)	Muscle strength (kg) unless specified	% Fat method	% Fat	Fat mass (kg) unless specified	LBM (kg)
Winnick et al. (2008) USA [28]	Whites RT AT African RT AT	Pre:Post Δ Time effect Group × time	98.1 ± 20.1:NR 99.1 ± 23.6:NR 109.5 ± 39.5:NR 99.5 ± 17.2:NR NR NR	35.1 ± 5.7:NR +2.6% 36.5 ± 6.6:NR −1.18% 33.6 ± 5.9:NR −2.6% 34.2 ± 5.9:NR −0.7% NR $P < 0.05$ RT African v Whites			DXA	40.2 ± 12.5:NR +1.38% 38.6 ± 9.3:NR −0.22% 38.5 ± 11.4:NR −0.85% 38.3 ± 9.8:NR −0.40% NR NS		
Baum et al. (2007) Germany [21]	RT Vib Flex	Pre:Post Δ Time effect Group × time	86.5 ± 14.7:NR −1.30 ± 2.36 Δ 83.3 ± 13.4:NR −0.86 ± 1.77 Δ 88.6 ± 24.1:NR −1.68 ± 4.57 Δ NS NR			NR:NR (Nm kg^{-1}) +14% Δ (left leg) NR:NR NR Δ NR:NR NR Δ NR NR				
Brooks (2007) USA [22]	RT Con	Pre:Post Δ Time effect Group × time		30.9 ± 6.13:NR NR Δ 31.1 ± 5.57:NR NR Δ NR	99.7 ± 12.81:NR NR Δ 100.1 ± 14.48:NR NR Δ NR NR	66 ± 22:90 ± 33^ +24 ± 11 Δ 338 ± 150:568 ± 189∨ +173 ± 106 Δ 62 ± 22:58 ± 22^ −4 ± 11 Δ 300 ± 156:285 ± 150∨ −19 ± 39 Δ NR $P < 0.001$	DXA		35.0 ± 12.25:NR NR Δ 33.7 ± 13.36:NR NR Δ NR NR	44.3 ± 9.47:45.5 ± 10.58 +1.1 ± 1.67 Δ 44.9 ± 10.58:44.8 ± 9.47 +0.4 ± 1.11 Δ NR $P = 0.04$
Sigal et al. (2007) Canada [27]	RT AT CT Con	Pre:Post Time effect Group × time	99.1 ± 30.4:98.0 ± 30.4 103.5 ± 31.0:100.9 ± 30.2 101.9 ± 30.4:99.3 ± 30.4 101.3 ± 28.6:101.0 ± 27.8 NR $P = 0.008$ AT v Con	34.1 ± 9.6:33.7 ± 9.6 35.6 ± 10.1:34.8 ± 10.1 35.0 ± 9.6:34.2 ± 9.6 35.0 ± 9.5:34.9 ± 8.7 NR $P = 0.009$ AT v Con	110 ± 24:107 ± 24 113 ± 23:110 ± 23 112 ± 24:108 ± 24 112 ± 24:111 ± 24 NR $P = 0.03$ AT v Con		Bioelectrical impedance	35.9 ± 9.6:35.0 ± 9.6 37.0 ± 9.3:36.3 ± 9.3 36.0 ± 9.6:35.0 ± 9.6 36.6 ± 8.7:36.9 ± 9.5 NR NS	36.5 ± 19.2:35.2 ± 19.2 39.2 ± 19.4:37.6 ± 19.4 37.6 ± 19.2:35.7 ± 19.2 38.0 ± 17.5:38.2 ± 17.5 NR $P = 0.44$ AT v Con	62.3 ± 13.6:62.5 ± 13.6 64.0 ± 13.9:63.0 ± 13.9 63.9 ± 13.6:63.2 ± 13.6 63.0 ± 12.7:62.5 ± 12.7 NR NS
Castaneda et al. (2006) Germany [29]	RT Con	Pre:Post Δ Time effect Group × time		32.1 ± 6.8:NR NR Δ 33.4 ± 6.3:NR NR Δ NR NR		NR:NR +43 ± 29% Δ* NR:NR +19 ± 31% Δ* NR $P = 0.01$				

Table 4 (*Continued*)

Author (year) country	Group	Type of change	Mass (kg)	BMI (kg m^{-2})	Waist circumference (cm)	Muscle strength (kg) unless specified	% Fat method	% Fat	Fat mass (kg) unless specified	LBM (kg)
Dunstan et al. (2006) Australia [25]	Cent Home	Pre:Post Δ Time effect Group × time	92.6 ± 17.1:NR −2.1 ± 3.4 Δ 91.2 ± 13.6:NR −2.2 ± 3.2 Δ $P < 0.05$ both grps NS	32.8 ± 4.8:NR NR Δ 32.4 ± 4.4:NR NR Δ NR NR	105.6 ± 11.7:NR −1.3 ± 5.3 Δ 107.4 ± 10.8:NR −2.0 ± 5.9 Δ NS NS	78.8 ± 43.9:NR^ −3.4 ± 17.8 Δ 29.9 ± 10.1:NR∨ −7.2 ± 10.5 Δ 78.3 ± 49.1:NR^ −3.7 ± 19.6 30.3 ± 12.0:NR∨ −0.3 ± 6.3 Δ $P < 0.05$ RT∨ $P < 0.05$ ∨	Bioelectrical impedance		37.6 ± 12.3:NR −0.8 ± 3.2 Δ 35.8 ± 10.0:NR −1.0 ± 3.2 Δ NS NS	55.0 ± 9.8:NR −1.3 ± 1.6 Δ 55.4 ± 10.5:NR −0.9 ± 2.2 Δ $P < 0.05$ both grps NS
Gordon et al. (2006) USA [26]	RT Con	Pre:Post Time effect Group × time	80 ± 19:NR 88 ± 15:NR NR NR	30.7 ± 6.2:31.3 ± 6.2 33.5 ± 6.2:33.4 ± 5.8 NR $P = 0.05$	100 ± 13.4:101 ± 10.8 108 ± 11.2:109 ± 12.4 NR $P = 0.43$					
Cauza et al. (2005) Austria [24]	RT AT	Pre:Post Δ Time effect Group × time	91.3 ± 13.6:90.2 ± 13.1 −1.1% Δ 96.7 ± 18.6:95.4 ± 18.6 −1.1% Δ NS NR	31.3 ± 4.2:30.9 ± 4.2 −1.1% Δ 33.9 ± 5.4:33.5 ± 5.4 −1.1% Δ NS NR		54.6 ± 16.0:68.6 ± 18.8^ +26% Δ 114 ± 36.6:168 ± 45.5∨ +48% Δ 43.9 ± 15.7:45.0 ± 16.1^ +2.5% Δ 93 ± 35.9:107 ± 42.1∨ +15% Δ $P < 0.001$ RT^ ∨, ET∨ NR	10 site skinfolds	44.5 ± 3.8:40.5 ± 5.2 −9.1% Δ 46.3 ± 3.3:44.5 ± 3.3 −3.4% Δ $P < 0.001$ both grps NR	39.6 ± 6.6:35.8 ± 8.0 −9.7% Δ 44.8 ± 9.5:42.5 ± 8.7 −5.3% Δ $P < 0.001$ both grps NR	49.4 ± 8.4:52.6 ± 8.0 +6.5% Δ 51.9 ± 10.3:52.9 ± 11.1 +2% Δ $P < 0.001$ RT NR
Cauza et al. (2005) Austria [23]	RT AT	Pre:Post Time effect Group × time		29.9 ± 2.3:29.9 ± 2.8 36.3 ± 12.4:36.3 ± 6.9 NS $P = 0.03$		47.4 ± 15.0:59.7 ± 18.4^ 31.8 ± 10.6:31.7 ± 10.6^ $P = 0.01$ RT, NS AT NR	NR		38.9 ± 6.5:33.5 ± 7.9 46.9 ± 10.6:44.4 ± 10.3 $P < 0.01$ both grps $P = 0.04$	46.3 ± 7.4:51.9 ± 9.1 56 ± 10.3:58.2 ± 11.1 $P < 0.01$ RT, $P = 0.03$ AT NR
Dunstan et al. (2005) Australia [20]	RT Con	Pre:Post Δ Time effect Group × time	88.7 ± 10.9:NR Unspecified increase 89.5 ± 12.1:NR Unspecified increase $P < 0.05$ RT NR		NR:NR −3.4 ± 4.7 Δ NR:NR −2.0 ± 4.3 Δ $P < 0.05$ RT NS	NR:NR +26.4 ± 22.8^ Δ +4.9 ± 6.4∨ Δ NR:NR −0.2 ± 19.1^ Δ −0.1 ± 5.4∨ Δ $P < 0.05$ RT^∨ $P < 0.05$^∨	DXA		33.1 ± 7.4:NR NR Δ 35.6 ± 6.8:NR NR Δ $P < 0.01$ both grps NR	51.8 ± 8.1:NR NR Δ 49.7 ± 9.5:NR NR Δ NS $P < 0.08$

Baldi and Snowling (2003) New Zealand [12]	RT	Pre:Post	112.3 ± 12.0:114.0 ± 12.3	34.3 ± 9.6:NR		NR/NR:NR/	Hydrostatic	32.4 ± 3.3:NR	38.1 ± 10.5:37.0 ± 10.5	74.3 ± 3.6:76.9 ± 3.3
	Con	Δ	110.3 ± 21.9:110.9 ± 22.2	36.4 ± 9.3:NR		NR(ext/flx)	weighing	30.7 ± 6.6:NR	37.7 ± 17.1:40.3 ± 18.9	72.6 ± 9.6:70.6 ± 9.0
		Time effect	$P < 0.05$ RT, NS Con	NR		+32.0/+3.2%^ Δ		NR	$P < 0.05$ Con	$P < 0.05$ RT, NS Con
		Group × time	NR	NR		+18.1%/+37.0%∨ Δ		NR	NR	NR
						NR/NR:NR/NR				
						NR/NR Δ				
						$P < 0.05$ RT^∨				
						NR				
Castaneda et al. (2002) USA [13]	PRT	Pre:Post	79.3 ± 17.8:79.5 ± 18.4		99.7 ± 12.8:97.5	389 ± 167:518	DXA		35.0 ± 12.3:34.0 ± 12.8	44.3 ± 9.5:45.5 ± 10.6
	Con	Δ	78.6 ± 17.3:79.4 ± 16.2		± 12.8	± 267*			33.7 ± 13.4:34.6 ± 12.3	44.9 ± 10.6:44.8 ± 9.5
		Time effect	NR		100 ± 14.5:102	+33 ± 7% Δ			NR	NR
		Group × time	$P = 0.89$		± 12.3	351 ± 173:299			$P = 0.26$	$P = 0.004$
					NR	± 167*				
					$P = 0.07$	−15 ± 3% Δ				
						NR				
						$P = 0.0001$				
Dunstan et al. (1998) Australia [15]	CRT	Pre:Post	83.6 ± 14.3:83.2 ± 14.3	28.3 ± 3.1:28.1 ± 3.1		NR:NR	7 site	NR	NR	NR
	Con	Δ	82.7 ± 12.8:83.7 ± 13.2	30.1 ± 3.8:30.4 ± 3.8		+15 ± 6%^ Δ	skinfolds			
		Time effect	NR	NR		+43 ± 12%∨ Δ				
		Group × time	$P < 0.05$	$P < 0.05$		NR:NR				
						NR^∨ Δ				
						$P < 0.05$^∨				
						NR				

RT, resistance training; Flex, flexibility training; Vib, vibration training; Con, control; Cent, centre-based training; AT, aerobic training; NS, not significant; PRT, progressive resistance training; CRT, circuit resistance training; ^, upper body; ∨, lower body; *, whole-body; ext, extension; flx, flexion; CT, combined aerobic and resistance training; NR, not reported.

compared to AT [23,24]. Seven non-RCT's [19,30–32,35,37,39] also reported muscle strength improved, with similar improvements in muscle strength observed in individuals with diabetes compared to those without diabetes [19,31]. One study also reported muscle power output improved over time [35]. Studies that reported greater improvements in muscular strength, utilized durations between 16 weeks [23,24,39] and 6 months [20] at moderate or moderate-high intensities. In contrast to other results, one study [32] reported highly significant ($P < 0.01$) increases in muscle strength after 6 weeks of moderate intensity RT. However, overall it appears that higher intensity RT is appropriate and more time efficient for muscle strength gains, although data evaluating lower intensity RT in patients with diabetes is limited (1/17 studies).

Improved glycemic control was observed in five [12,13,22,24,26] of the 10 papers from RCT's (3 studies) that reported significant improvements in strength, while four RCT's [15,21,22,24,26] that increased strength also improved insulin sensitivity, leaving two RCT's [12,20] that did not improve insulin sensitivity despite increasing strength. In non-RCT's, no studies that improved strength reported improved glycemic control, yet four studies [19,30,37,39] that improved strength reported improved insulin sensitivity and two of six studies [31,32] did not improve insulin sensitivity.

9. Body composition

9.1. *Lean body mass*

Lean body mass (LBM) was measured by dual energy X-ray absorptiometry (DXA) in four studies [13,20,22,30,40] including two RCT's [13,20,22], or estimated after accounting for fat mass in a further six studies [12,24,25,27,32,33,37] including four RCT's [12,24,25,27], with one study [23] not specifying the method used (Table 4). Results varied, with significant LBM increases of 3–6 kg with RT [12,23,24] and 2 kg with AT [23]. Two studies reported significant ($P < 0.05$; $P = 0.04$) [13,22] or a trend ($P < 0.08$) [20] towards improvements for LBM when RT was compared with the non-exercising control group.

9.2. *Fat mass*

Fat mass was typically determined through mathematical equations after measuring body mass and using various techniques to estimate percentage fat. Significant decreases in fat mass of 1–4.5 kg with RT [20,23,24,32,39] and 2 kg with AT [23,24] occurred over the training duration (Table 4). One study [12] reported no changes in fat mass with RT, compared with a 3.5 kg increase ($P < 0.05$) in controls over 10 weeks. With the exception of one study [32], interventions with durations less than 10 weeks did not report fat mass (Table 4). The current evidence suggests that moderate or high intensity training of greater than 10 weeks tends to reduce fat mass in individuals with diabetes.

9.3. *Percentage body fat*

One non-RCT [30] reported a decrease in percentage body fat as measured by DXA. With one RCT [28] and one non-RCT [40]

reporting no change. Percentage body fat results were not reported in other studies despite utilizing DXA [13,20,22]. Two further studies [12,37] utilized hydrostatic weighing, reporting no evidence of change to percentage body fat (Table 4). Bioelectrical impedance was used in three studies [25,27,32], with changes only reported when AT was compared to controls ($P = 0.008$) [27] (Table 4). Four studies utilized the less sensitive measure of skin-fold measurements where decreases in body fat of up to 9.1% were reported (Table 4). One non-RCT [35] reported percentage body fat results, but not how it was measured.

9.4. *Body mass*

Typically there was no change in body mass with any exercise regimen, however, one study [12] reported a 2 kg increase ($P < 0.05$) after 10 weeks of moderate intensity RT (Table 4). After 6 months of home-based maintenance [20], body mass significantly increased ($P < 0.05$), although final levels remained lower than baseline.

9.5. *Girth measures*

Measures of waist circumference were not routinely completed (7/20 studies; Table 4) [13,20,22,25–27,32,38,40] with change occurring when comparing sedentary controls with RT [13], AT [27] and over time with RT [20,40]. Waist circumference was reported to remain decreased after 6 months of home-based RT maintenance [20].

10. Cardiac risk factors

10.1. *Lipid profile*

Blood lipids were reported in nine studies with general improvements in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides reported after RT ($P < 0.001$; $P < 0.01$) [24,36,40].

10.2. *Blood pressure*

Blood pressure was measured in 10 studies. Three studies reported beneficial changes in systolic blood pressure associated with all forms of training [13,21,24]. Improvements to diastolic blood pressure were less frequently observed, but still occurred over time with RT and AT [24].

11. Discussion

Individuals with diabetes are able to complete RT with minimal risk of negative health outcomes or injury, while improving overall glycemic control, insulin sensitivity and muscular strength. Overall, the quality of study design was good with 13 papers reporting on 10 RCT's, of which all but three were published since 2005. The major findings from these studies are that completing RT, and AT over extended durations will result in similar improvements to glycemic control [23,27]. However, RT could potentially provide greater benefits in terms of glycemic control than AT with researchers and practitioners intimating that RT, comprising short bouts with intermittent rest periods, is better tolerated than AT [10,44,45]. To further improve the quality of studies and knowledge in this area and to enable comprehensive comparison between studies in the future, consideration needs to be given to quantifiable and replicable exercise prescriptions, specifying how missing data is treated and determining sample sizes by power calculations.

A clinically relevant lowering of HbA1c, a key marker of improved long-term glycemic control, was reported in a number of RT studies while those reporting no effect were intervention studies with durations of 10 weeks or less. These changes appear to be of a similar or greater magnitude to aerobic training [23,24,27], however the effect of combining RT with AT remains unclear with only one study [27] making a direct comparison between combined training and isolated RT or AT interventions.

Interestingly, insulin sensitivity was only evaluated using the euglycemic–hyperinsulinemic clamp in non-RCT's [19,30]. These studies reported increased insulin sensitivity following RT, despite the time that the measure was performed varying from 16 to 48 h following the final exercise session and the intensity and frequency of the training varying markedly. Other, less precise measures of insulin sensitivity, generally indicated improvements at times ranging from 24 to 72–96 h [21,40] following the final RT session of a long-term training program. However, the effect of a single session of RT on insulin sensitivity in previously untrained subjects has not been investigated beyond 12–24 h after the session [32,33]. This raises questions about the training frequency that should be prescribed, which is currently based on improvements to HbA1c. Eight RCT's included in this systematic review [12,15,20–22,24–26,28] present HbA1c and insulin sensitivity data, with only one [12] indicating that insulin sensitivity did not improve when HbA1c improved. Furthermore, two studies [15,21] indicated that insulin sensitivity improved but was not reflected in HbA1c, which did not change. Additionally, insulin sensitivity improved after 12 months of gym-based maintenance despite glycemic control becoming worse [25]. Therefore, further investigations as to whether RT should be prescribed based on insulin sensitivity should be undertaken. If RT should be prescribed based on insulin sensitivity, RT may need to be prescribed everyday in this population, at least initially, as the length of time insulin sensitivity remains improved following a single RT session has not been adequately evaluated. After 12–16 weeks of training, improved insulin sensitivity appears to be maintained for 4–5 days [21,22,26], therefore glucose control may potentially be improved or maintained with one or two RT sessions each week. Both of these possibilities vary considerably from current RT recommendations of 3 days/wk [6]. It is possible that RT should be performed more regularly initially to improve insulin sensitivity and glycemic control, before it can be performed less frequently to maintain the benefits; however this is yet to be thoroughly examined.

The training environment and intensity of RT also need further investigation, as decreased compliance to the training protocol appears to be associated with a decline in insulin sensitivity as demonstrated by the lower adherence level and

increased insulin resistance reported with home-based training [20,25]. While high adherence to RT protocols resulted in significant muscle strength improvements, changes in body mass were generally not observed. In contrast, LBM increased and percentage body fat decreased, confirming that body composition is improved with RT. Therefore, RT may provide further benefits for individuals with diabetes attempting to lose weight as RT may counteract the loss of muscle mass typically associated with isolated hypocaloric diets [46]. However, changes to body composition are unlikely to account for any changes in insulin sensitivity, as this can be increased following a single exercise session [32,33]. Although changes to body composition may not improve insulin sensitivity, individuals with diabetes are at an increased risk of cardiac co-morbidities for which improved body composition would reduce this risk. Additionally, RT has the ability to improve muscle quality (defined as a functional measure of strength per unit volume of muscle) and change the characteristics of a muscle fibre [22,47], suggested to result in increased glucose transport. Although, limited data from individuals with diabetes suggest that muscle mass or body composition changes do not influence insulin sensitivity, local contraction-mediated responses from RT might [19], resulting in increased intracellular signalling [10] leading to increased membrane bound GLUT4 transporters and improved insulin sensitivity. Despite mechanisms for why RT improves insulin sensitivity not yet being fully elucidated, they are understood to have some common mechanisms to AT as well as some unique adaptations attributable to RT alone [7,37].

Although not reviewed in detail here, RT invokes many health benefits for individuals with diabetes in addition to improved glycemic control. These include improvements in bone strength, minimization of sarcopenic losses or muscle weakness associated with aging, improved balance and reduced falls risk [48]. The beneficial effects of RT on lowering cardiovascular risk (i.e. blood pressure and blood lipids) have been reviewed elsewhere [4]. Of the studies reviewed here, the impact of RT on lipid profiles is minimal in individuals who were normal or just above normal at baseline, but it is promising that beneficial blood pressure effects have been reported in hypertensive patients with type 2 diabetes [13,21,24]. Decreasing body mass by dieting (energy restriction) has detrimental effects on muscle mass and while AT is only able to maintain the integrity of muscle [49] it is suggested that RT is able to counteract these detrimental effects in a way that AT cannot by actually improving the amount and integrity of muscle mass [46].

Compelling evidence from both RCT's and non-RCT's is that RT is safe for individuals with diabetes who are likely to have complex co-morbidities, although it needs to be noted that all studies to date have excluded patients with contraindications to RT [50]. Resistance training is effective in improving glycemic control and increasing insulin sensitivity. Higher intensity and longer intervention duration of RT appear most beneficial, but this along with training frequency, are parameters that require further investigation. It is likely that individualized programs, taking into account an individual's current level of strength, severity of diabetes and also co-morbidities will optimise the adaptive response and enhance compliance. Determining the minimum effective dose of RT, or if appropriate in conjunction with AT, would possibly improve ongoing compliance, and therefore lead to improved health outcomes. Resistance training has been shown to not only be equivalent to AT in ameliorating diabetes and its associated complications; it may also be the exercise of choice for individuals with diabetes or pre-diabetes who find adherence to continuous moderate intensity aerobic training too physically challenging.

Conflict of interest

The authors declare that they have no conflict of interest.

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Diabetes Research and Clinical Practice

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International Diabetes Federation

Brief report

Reproducibility of multiple repeated oral glucose tolerance tests

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ARTICLE INFO

Article history:
Received 10 August 2011
Received in revised form
26 August 2011
Accepted 27 August 2011
Published on line 25 September 2011

Keywords:
Apparently healthy
Glucose tolerance
Insulin sensitivity
Hyperinsulinaemia
OGTT

ABSTRACT

We assessed the oral glucose tolerance test's (OGTT) ability to produce consistent results for estimating insulin sensitivity over four consecutive days. Individual coefficients of variation for OGIS and Stumvoll-ISI were 7.8% and 14.4% with no statistically significant difference between days. Thereby, indicating repeated OGTT's are reliable for estimating insulin sensitivity.

1. Introduction

Insulin sensitivity is regularly estimated through the use of an oral glucose tolerance test (OGTT) with a number of equations showing good correlation with the gold standard method, the euglycaemic hyperinsulinaemic clamp [1]. However, issues concerning glucose load (50–100 g), reproducibility and diurnal variation of the OGTT have been reported [2], with reliability questioned [3,4]. Reproducibility investigations have centred on variables around the testing conditions, including glucose load [5], time of day (6), and the fasting period prior to testing [6,7]. And while many studies have reported variations in glucose response from multiple or repeated OGTT's [3,4,6,8], none have looked at the reproducibility of OGTT's repeated on consecutive days. So in light of this, we believed it important to analyse the glucose and insulin responses in apparently healthy individuals to determine whether OGTT's are reliable to estimate insulin sensitivity on consecutive days. Therefore, the aim of this study was to investigate whether insulin sensitivity was affected by repeated daily OGTT's.

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Abbreviations: OGTT, oral glucose tolerance test; AUC, Area under the curve; OGIS, oral glucose insulin sensitivity index; ISI, insulin sensitivity index.

0168-8227/$ – see front matter
doi:10.1016/j.diabres.2011.08.025

2. Materials and methods

2.1. Participants and study design

Ten sedentary, apparently healthy individuals with no diagnosed metabolic conditions took part in this trial. Inclusion criteria were: aged 40–69 years, taking no medications influencing metabolism, and not having participated in resistance training in the last six months or undertaking regular aerobic exercise. Exclusion criteria included: recent coronary event or established heart disease, uncontrolled hypertension (>150/90 mm Hg), neuropathy and being unable to understand English or follow instructions. Participants completed the self-report International Physical Activity Questionnaire [9] and were instructed not to complete any structured or specific exercise during the study, record all food consumed in a food diary and replicate their diet before each OGTT. Participant characteristics are presented in Table 1.

Participants arrived at the research facility between 6 am and 9 am by private vehicle, following a 12-h overnight fast. Anthropometric measurements and a fasting blood sample were collected before participants undertook an OGTT to obtain baseline glucose and insulin responses [10]. Participants then returned to the research facility to undergo further OGTT's on the three subsequent mornings.

2.2. Blood sampling and analysis

A cannula was inserted into an antecubital vein with blood samples obtained before consuming 75 g of glucose in 300 mL of water (Gluco Scan, BIOCORP Aust Pty. Ltd.). Further blood samples were collected at 30, 60, 90 and 120 min after consuming the glucose, with patency maintained by flushing with saline, and the first 2 mL of blood collected being discarded. The study protocol is presented schematically in Fig. 1 and was approved by the RMIT University Human Research Ethics Committee with written informed consent obtained prior to participation. Lipid profiles and glycaemic control (HbA1c) were measured in a commercial laboratory. Glucose and insulin were measured using the YSI 2300 Stat Plus analyser (Yellow Springs, USA) and Millipore human insulin ELISA kits respectively. Area under the curve (AUC) was calculated by a computer-based trapezoidal model and insulin sensitivity estimated by the oral glucose insulin sensitivity (OGIS) index [11] and the Stumvoll insulin sensitivity index (ISI) equation [12].

Table 1 – Participant demographics.

Outcome measure (units)	Mean (SD)
Male/female	3/7
Age (years)	54.6 (6.5)
Weight (kg)	93.4 (16.4)
Height (cm)	167.7 (6.8)
BMI (kg m^{-2})	33.3 (6.3)
Waist circumference (cm)	98.8 (12.6)
Waist:hip	0.88 (0.08)
SBP (mm Hg)	126 (14)
DBP (mm Hg)	83 (10)
Cholesterol (mmol L^{-1})	4.9 (1.2)
LDL-C (mmol L^{-1})	2.8 (1.0)
HDL-C (mmol L^{-1})	1.42 (0.24)
Triglycerides (mmol L^{-1})	1.6 (0.5)
HbA1c (%)	5.5 (0.3)
Glucose (mmol L^{-1})	5.3 (0.3)
Insulin (pmol L^{-1})	130.1 (82.1)
Activity (MET-min wk^{-1})	1428 (1365)
Sedentary time (min)	435 (207)

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HbA1c, glycated haemoglobin; MET, metabolic equivalents.

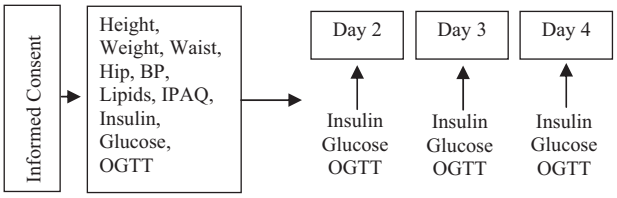

Fig. 1 – Study protocol.

2.3. Statistical methods

All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of $p = 0.05$ and a Bonferroni correction made for multiple analyses. A repeated measures analysis of variance (ANOVA) was completed to determine change over time of the overall outcomes and to determine the reliability of the change scores from each independent time-point for each repeated measure. Change was calculated by subtracting the follow-up score from the initial score and to provide an indication of repeatability, coefficient of variation (CV) was calculated for each individual by dividing the standard deviation of their results from their four tests by their mean result. Data are presented as means (95% confidence intervals (CI)) unless otherwise indicated. Approximately 4% of glucose and insulin data points were missing (due to occlusions within the cannula) and were substituted by bringing the last known value for that time point forward to ensure AUC was calculated from five time-points [13].

3. Results

We failed to detect any statistically significant change in glucose or insulin response or insulin sensitivity over the 4-days of repeated, daily OGTT's (Table 2; $p = 0.20$). There were also no significant differences in the change scores for glucose AUC ($p = 0.37$), insulin AUC ($p = 0.22$), OGIS ($p = 0.41$) or Stumvoll ISI ($p = 0.12$; Table 3).

At baseline, two participants were considered to have extreme hyperinsulinaemia (insulin ≥200 pmol L^{-1}). One individual with extreme hyperinsulinaemia was classified as having impaired glucose tolerance (2-h glucose ≥7.8 mmol L^{-1}) 1) using the World Health Organisation criteria [10] at baseline, 24-h and 48-h testing, before reverting to a classification of normal glucose tolerance at the final test. At baseline, all other

Table 2 – Glucose, insulin and insulin sensitivity response to consecutive OGTT's. Mean (95% confidence interval).

Outcome	Baseline (0 h)	24 h	48 h	72 h
N = 10				
2-h glucose (mmol L^{-1})	6.2 (5.1–7.3)	5.8 (4.4–7.2)	5.9 (4.7–7.1)	5.9 (4.8–7.1)
Glucose AUC (mmol L^{-1} 120 min^{-1})	855.7 (741.3–970.2)	839.6 (690.1–988.6)	882.7 (706.3–1059.1)	866.2 (674.6–1057.7)
2-h insulin (pmol L^{-1})	743.1 (214.0–1272.2)	676.1 (150.7–1201.5)	729.5 (213.2–1245.9)	595.6 (184.1–1007.1)
Insulin AUC (pmol L^{-1} 120 min^{-1})	91,851 (43,944–139,759)	142,206 (18,470–265,941)	122,431 (40,811–204,051)	104,306 (54,934–153,677)
OGIS (mL min^{-1} m^{-2})	333.6 (282.2–385.0)	351.8 (275.2–428.4)	373.0 (309.7–436.3)	372.9 (299.7–446.1)
Stumvoll ISI (arbitrary units)	0.047 (0.003–0.091)	0.051 (0.007–0.095)	0.046 (0.002–0.089)	0.056 (0.020–0.092)
N = 8				
2-h glucose (mmol L^{-1})	5.8 (4.9–6.7)	5.8 (4.3–7.3)	5.8 (4.7–6.8)	5.9 (4.6–7.3)
Glucose AUC (mmol L^{-1} 120 min^{-1})	835.0 (720.3–949.8)	826.3 (675.5–977.1)	873.7 (703.5–1043.9)	870.0 (653.8–1086.2)
2-h insulin (pmol L^{-1})	531.7 (71.4–992.0)	516.4 (96.1–936.7)	586.2 (119.4–1052.9)	486.6 (134.7–838.5)
Insulin AUC (pmol L^{-1} 120 min^{-1})	62,672 (40,630–84,714)	62,584 (38,235–86,933)	77,443 (40,909–113,976)	85,505 (34,296–136,713)
OGIS (mL min^{-1} m^{-2})	354.0 (301.3–406.7)	379.8 (318.8–440.7)	363.8 (282.1–445.4)	377.5 (300.9–454.1)
Stumvoll ISI (arbitrary units)	0.067 (0.028–0.106)	0.068 (0.027–0.108)	0.061 (0.018–0.104)	0.069 (0.035–0.104)

AUC, area under the curve; OGIS, oral glucose insulin sensitivity index; ISI, insulin sensitivity index.

individuals were considered to have normal glucose tolerance however, impaired glucose tolerance classifications were present for one individual at the second OGTT (2-h glucose = 8.7 mmol L^{-1}) and a different individual at the final OGTT (2-h glucose = 8.0 mmol L^{-1}).

The glucose, insulin and insulin sensitivity responses are presented in Fig. 2 and clearly show that as a group, the response is similar from test to test. However, the individuals with hyperinsulinaemia clearly respond differently and have marked variation in their response. When only those with normal fasting insulin levels at baseline were considered (N = 8), the change scores were generally smaller and were still similar for glucose AUC ($p = 0.17$), insulin AUC ($p = 0.41$), OGIS ($p = 0.15$) and the Stumvoll ISI ($p = 0.34$). Effect sizes (partial eta squared) of these changes were large [14], with values of 0.608, 0.410, 0.625 and 0.461 respectively. Excluding the individuals with extreme hyperinsulinaemia, the mean (range) coefficient of variation for individuals from day to day was 6.3% (1.1–13.4%), 20.6% (6.8–48.0%), 7.8% (4.2–14.2%) and 14.4% (0.3–43.3%) for glucose AUC, insulin AUC, OGIS and Stumvoll ISI respectively.

The clinically relevant change (calculated by the change from the first test to the second ± the 95% CI) in the response to an OGTT in apparently healthy individuals for glucose and insulin response along with insulin sensitivity is presented in Table 3. From a practical perspective, if these

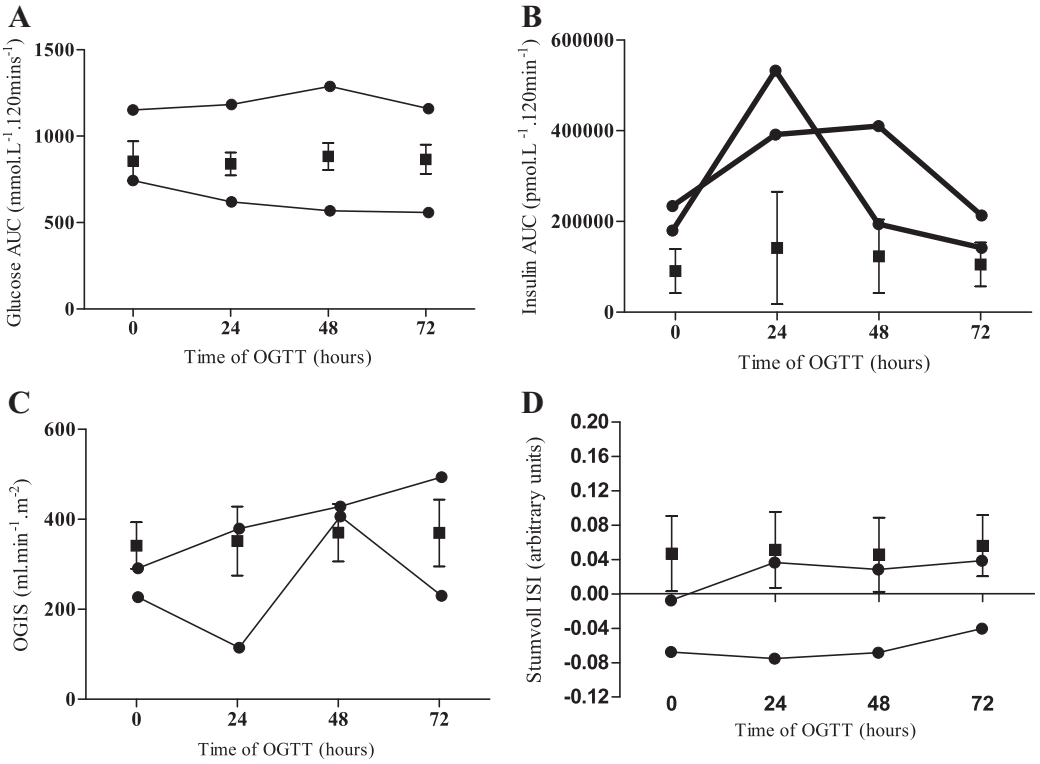

Fig. 2 – Mean (■) and 95% CI for glucose AUC (A), insulin AUC (B), OGIS (C) and Stumvoll ISI (D) with individual responses of participants (n = 2) with extreme hyperinsulinaemia plotted (●) to show the variation.

Table 3 – The observed change (variation) for each repeated measure for Glucose and Insulin AUC and insulin sensitivity. Mean (95% CI).

Outcome	Change 1	Change 2	Change 3	Change 4	Change 5	Change 6
N = 10						
Glucose AUC (mmol L^{-1} 120 min^{-1})	−16.1 (−77.6–45.4)	27.0 (−56.5–110.4)	10.4 (−94.2–115.0)	43.1 (−1.4–87.5)	26.5 (−57.3–110.4)	−16.6 (−75.1–42.0)
Insulin AUC (pmol L^{-1} 120 min^{-1})	50354.3 (−32581.7–133290.3)	30579.4 (−7999.9–69158.7)	12454.3 (−18172.3–43080.9)	−19774.9 (−99968.1–60418.3)	−37900.0 (−139828.4–64028.4)	−18125.1 (−70054.3–33804.1)
OGIS (mL min^{-1} m^{-2})	18.2 (−22.8–59.2)	39.4 (−16.4–95.2)	39.3 (−7.7–86.3)	21.2 (−51.2–93.6)	21.1 (−19.4–61.6)	−0.1 (−52.1–51.9)
Stumvoll ISI (arbitrary units)	0.004 (−0.008–0.016)	−0.001 (−0.013–0.011)	0.009 (−0.004–0.022)	−0.006 (−0.012–0.001)	0.005 (−0.006–0.016)	0.010 (0.001–0.020)
N = 8						
Glucose AUC (mmol L^{-1} 120 min^{-1})	−8.7 (−80.9–63.5)	38.7 (−44.4–121.7)	35.0 (−87.3–157.3)	47.4 (0.4–94.4)	43.7 (−61.7–149.1)	−3.7 (−72.0–64.7)
Insulin AUC (pmol L^{-1} 120 min^{-1})	−88.1 (−7237.1–7060.9)	14770.6 (−3586.9–33128.1)	22832.9 (−11855.2–57520.9)	14858.8 (−1571.5–31289.0)	22921.0 (−12737.0–58579.0)	8062.3 (−23063.2–39187.7)
OGIS (mL min^{-1} m^{-2})	25.7 (−1.2–52.7)	9.8 (−33.5–53.0)	23.5 (−6.6–53.6)	−16.0 (−43.6–11.6)	−2.3 (−28.7–24.2)	13.8 (−19.1–46.6)
Stumvoll ISI (arbitrary units)	0.001 (−0.008–0.010)	−0.006 (−0.016–0.004)	0.002 (−0.007–0.011)	−0.007 (−0.014–0.001)	0.001 (−0.009–0.012)	0.008 (−0.002–0.019)

AUC, area under the curve, OGIS, oral glucose insulin sensitivity index, ISI, insulin sensitivity index, change 1, 24 h minus baseline, change 2, 48 h minus baseline, change 3, 72 h minus baseline, change 4, 48 h minus 24 h, change 5, 72 h minus 24 h, change 6, 72 h minus 48 h.

confidence intervals are converted into unit values, they would infer that glucose AUC increases of greater than 63.5 mmol L^{-1} 120 min^{-1} and decreases of greater than 80.9 mmol L^{-1} 120 min^{-1} exceed the combined daily measurement and biological variation and can therefore be viewed with confidence as indicating real unfavourable and favourable changes respectively. The same can be applied to insulin AUC increases of greater than 7061 pmol L^{-1} 120 min^{-1} and decreases of greater than 7237 pmol L^{-1} 120 min^{-1} indicating real unfavourable and favourable changes respectively, with real unfavourable and favourable changes for OGIS respectively being a decrease of greater than 1.2 mL min^{-1} m^{-2} and an increase of greater than 52.7 mL min^{-1} m^{-2}. The real unfavourable and favourable changes for Stumvoll ISI are a decrease of greater than 0.008 index units and an increase of greater than 0.010 index units respectively.

4. Discussion

The OGTT has previously been reported to have unsatisfactory reproducibility in apparently healthy individuals [4] and those with mild diabetes [3] when the tests were repeated within two and seven days. We have shown in this study that the glucose and insulin response in apparently healthy individuals without hyperinsulinaemia is quite consistent and produced reliable results for insulin sensitivity (OGIS CV = 7.8%, Stumvoll ISI CV = 14.4%) from consecutive, repeated OGTT's. However, our cases of individuals who exhibited hyperinsulinaemia in order to maintain glucose homeostasis, suggest that repeated OGTT's may not produce a reliable estimation of insulin sensitivity for people with pre-diabetes and diabetes. This is an important finding and to the best of our knowledge, is something that has not been reported previously. We are therefore able to suggest through our small study of apparently healthy individuals without hyperinsulinaemia that the OGTT appears to be an appropriate method to estimate and measure change in insulin sensitivity over time, but other methods might be more appropriate for individuals with impaired glucose metabolism.

Funding

This research was completed using internal research funding.

Acknowledgments

We would like to acknowledge Seymour Health for facilitating part of this research in allowing some testing procedures to be carried out there. We are also gratefully indebted to the participants who volunteered for this project.

Brett Gordon is supported by a RMIT University, School of Medical Sciences, research scholarship.

Conflict of interest

There are no conflicts of interest.

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J. Endocrinol. Invest. First published ahead of print September 30, 2011 as DOI: 10.3275/7972

Title:

Insulin sensitivity in response to a single resistance exercise session in apparently healthy individuals.

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Running Title:

Insulin sensitivity and resistance exercise

Submitted: June 24, 2011
Accepted: August 1, 2011

Key Words:

Exercise Therapy; Glucose Tolerance Test; Health; Glucose Intolerance; Training Frequency

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Acknowledgments

The authors would like to thank Assoc Prof Jeff Walkley and Mr David Opar for contributing their time to conduct the dual x-ray absorptiometry scans. We are also gratefully indebted to the participants who volunteered for this project. The authors have no competing interests and this study was completed using internal department research funding.

List of Abbreviations

OGTT = oral glucose tolerance test

AUC = area under the curve

OGIS = oral glucose insulin sensitivity

HbA1c = glycated haemoglobin

DXA = dual x-ray absorptiometry

1RM = one repetition maximum

IPAQ = international physical activity questionnaire

CI = confidence interval

J. Endocrinol. Invest. First published ahead of print September 30, 2011 as DOI: 10.3275/7972

Abstract

Background: Regular resistance exercise completed for a number of weeks has been shown to increase insulin sensitivity and reduce the risk of diabetes related complications. However, the acute responses to resistance exercise have not been adequately investigated in relation to training frequency.

Aim: To investigate the changes to insulin sensitivity in apparently healthy individuals following a single session of unaccustomed resistance exercise.

Subjects and Methods: Ten sedentary, apparently healthy individuals performed a baseline oral glucose tolerance test and maximal strength testing. Participants then performed a single session of moderate-high intensity resistance exercise which was followed by four consecutive days of oral glucose tolerance testing, for which participants replicated their initial diet. Mean estimated insulin sensitivity change scores from baseline values and their 95% confidence intervals were compared to the previously determined values for a clinically meaningful change.

Results: Two participants were identified as having hyperinsulinaemia and their data were therefore removed from the main analysis. There was a clinically meaningful increase in insulin response (mean >7,237 $pmol.L^{-1}.120mins^{-1}$) on all days following the exercise session and a clinically meaningful increase in glucose response (mean >81 $mmol.L^{-1}.120mins^{-1}$) on only the third day following exercise. These changes suggest a potentially adverse short-term effect. Additionally the two individuals with hyperinsulinaemia displayed more extreme results.

Conclusion: These results suggest that insulin sensitivity may be impaired following a single session of unaccustomed resistance exercise for approximately four days in healthy untrained, older individuals. Further research is required for individuals with hyperinsulinaemia.

Introduction

Insulin resistance is a condition where the tissues (specifically skeletal muscle and the liver) are less responsive or sensitive to insulin, resulting in decreased glucose uptake. This results in increased insulin secretion and abnormally high levels of circulating insulin (hyperinsulinaemia) in an attempt to maintain glucose homeostasis (1). Insulin resistance has been associated with low grade inflammation that has been reported in obesity (2) and is a risk factor for hypertension and type 2 diabetes (3, 4). This condition is distinct from overt type 2 diabetes, where the pancreas is unable to adequately increase insulin secretion to account for the decreased insulin action (1).

Chronic exercise training, in the form of moderate-intensity aerobic type activities is known to reduce fasting glucose levels, improve glycated haemoglobin levels (HbA1c) and increase insulin sensitivity (5). More recently, resistance training has been identified as a modality that is also capable of improving glucose levels and insulin sensitivity, as well as being associated with other health benefits such as improved body composition, blood pressure, lipid profiles and bone strength (6). In relation to metabolic health, it is accepted that higher intensity resistance training is of greater benefit than lower intensity training, however the required frequency to maintain or continue these improvements remains unclear (7).

In the context of insulin sensitivity and glucose homeostasis, there have been few studies that have investigated the acute effects of resistance exercise in healthy individuals (8-10) and/or those with type 2 diabetes (11, 12). In those studies that have been published, the results are equivocal, with some reporting increased insulin sensitivity 24 hours after a single session of resistance exercise (13), and increased insulin action approximately 36 hours after unaccustomed eccentric resistance exercise (14). However, Howlett and colleagues (9) refute these findings, suggesting that a single bout of resistance exercise impairs insulin action.

Furthermore, the ongoing effects of a single bout of resistance exercise are unknown, with no studies tracking the insulin or glucose response beyond 36 hours following the exercise bout. Without such knowledge it is difficult to determine the optimal rest interval between acute bouts of resistance exercise and hence, the optimal training frequency. This is an important consideration for middle-aged adults who are more commonly at risk of developing diabetes and often have the perception of having decreased time available to exercise between work and family commitments (15).

It was therefore the aim of this study to investigate the insulin sensitivity response using oral glucose tolerance tests administered on each of the four days following a single bout of moderate-high intensity resistance exercise, to determine the period of time that any changes were present.

Methods

Ten sedentary (completing less than 20 minutes of aerobic exercise twice weekly), apparently healthy males (n=3) and females (n=7) with a mean (SD) age of 51.6 (5.8) years with no diagnosed metabolic conditions were enrolled to participate. Ethical approval was granted from the RMIT University and Austin Health Human Research Ethics Committees, and all participants provided written informed consent. This study conformed to the principles of the Declaration of Helsinki. Inclusion criteria were: aged 40-69 years, taking no medications influencing metabolism, and not having participated in resistance training in the last six months. Exclusion criteria included: recent coronary event or established heart disease, uncontrolled hypertension (>150/90 mmHg), neuropathy, orthopaedic disorder preventing them from completing resistance training, any medical condition that contraindicated resistance training, and being unable to understand English or follow instructions.

All participants arrived at the research facility between 0600 and 0900 hours by the use of private vehicles, following a 12-hour overnight fast and had height (QuickMedical

stadiometer to the nearest 0.1cm), weight (Tanita, BWB-600, to the nearest 0.1kg), waist and hip girth (using a standard non-elastic tape, to the nearest 0.5cm) measured. They also had a fasting blood sample collected before undergoing an oral glucose tolerance test (OGTT) according to world health organisation protocols to obtain baseline glucose and insulin responses (16). The OGTT was conducted by inserting a canulla into an antecubital vein with blood samples obtained before consuming 75g of glucose mixed in 300ml of water (Gluco Scan, BIOCORP Aust Pty. Ltd.). Further blood samples were collected at 30, 60, 90 and 120 minutes after consuming the glucose, with patency maintained by flushing with saline every 15 minutes. The first 2ml of blood collected was discarded to ensure there was no saline in the sample. The study protocol is presented schematically in Figure 1.

Participants returned to the research facility three to four days after their initial OGTT and underwent dual x-ray absorptiometry (DXA) before being familiarised with the resistance exercise equipment. Participants then underwent one repetition maximum (1RM) testing on all five exercises to be included in the resistance exercise bout. One repetition maximum testing followed a set protocol as reported previously (12). Following a 13-14 day wash-out period, participants returned to the research facility to undergo the resistance exercise bout consisting of three sets of 10 repetitions for five whole-body exercises (bench press, 45˚ leg press, shoulder press, 45˚ calf raises and lateral pull-down) at 45%, 60% and 75% of 1RM. The resistance training protocol was based on protocols used in similar previous research (8, 12). Participants returned to the research facility after a 12-hour overnight fast to complete an OGTT for each of the next four days following the exercise session.

Participants completed the self-report International Physical Activity Questionnaire (IPAQ) (17) prior to beginning the study to assess activity levels. Participants were asked to record all food consumed throughout the study period in a food diary (with an example provided) and were instructed to replicate their diet before each OGTT. Nutritional analysis was conducted by the same researcher on the FoodWorks 2007 (Xyris software (Australia) Pty Ltd.,

xyris.com.au) dietary analysis computer program version 5, service pack 1, to compare total energy consumed and the volume (grams) of protein, fat and carbohydrate each day.

Baseline fasting blood samples were collected in serum separator tubes and an EDTA containing tube. These were sent to a commercial laboratory for analysis of lipid profiles (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides with laboratory variability levels of 2%, 9%, 12% & 3.5% respectively) and glycated haemoglobin (HbA1c – laboratory variability of 3%). Additional samples were also collected into serum separating tubes and tubes containing fluoride oxalate, and allowed to clot on ice before being centrifuged for seven minutes at 5000 rpm at 4˚C. Aliquots of serum and plasma were frozen at -80˚C for later analysis of insulin and glucose respectively. Fasting, 30, 60, 90 and 120 minute plasma samples were analysed for glucose using the YSI 2300 Stat Plus analyser (Yellow Springs, USA) in duplicate with a coefficient of variation of <1%. Corresponding serum samples were analysed for insulin using Millipore human insulin ELISA kits in duplicate with a coefficient of variation of 10%. Insulin sensitivity was determined using glucose and insulin area under the curve (AUC) calculated by a computer-based trapezoidal model using GraphPad Prism 5 for Windows (Version 5.01, La Jolla, CA) and calculated using the oral glucose insulin sensitivity (OGIS) index (18).

All data were analysed using SPSS version 18 for Windows (SPSS, Chicago, IL) with significance set at an alpha level of p=0.05. Change scores for glucose and insulin response along with OGIS were calculated by subtracting the follow-up value from the baseline value. The mean change scores at each time-point were then compared with the predetermined (Gordon, et al., unpublished data) clinically meaningful change to determine its relevance. A repeated measures analysis of variance (ANOVA) was completed for nutritional components to determine change over time. Data are presented as means (95% confidence intervals [CI]) unless otherwise indicated. Approximately 3% of data points were missing (due to occlusions within the canulla) and were substituted by bringing the last known value for that time-point

forward (19) for 30 minute glucose and insulin (two and one occasions respectively), 60 minute glucose and insulin (one occasion), 90 minute glucose and insulin (three occasions) and 120 minute glucose and insulin (one occasion), ensuring that AUC was calculated from five time-points. On one occasion, the 60 minute sample of the baseline test was unable to be collected, resulting in the AUC for that individual at that time being calculated on four time-points instead of five.

Results

While being categorised as having normal glucose tolerance by the baseline OGTT, one individual was identified as having hyperinsulinaemia (130<insulin<200 pmol.L^{-1}) at baseline, and another identified as having extreme hyperinsulinaemia (insulin ≥200 pmol.L^{-1}) at baseline. The individual with hyperinsulinaemia experienced a potentially unfavourable reduction (64 ml.min^{-1}.m^{-2}) to insulin sensitivity, according to OGIS, 24 hours after exercise before returning to baseline and showing no additional change, while the individual with extreme hyperinsulinaemia experienced a beneficial increase to insulin sensitivity through OGIS of between 66 ml.min^{-1}.m^{-2} and 128 ml.min^{-1}.m^{-2} at all follow-up time-points. These two participants (one male and one female) were therefore excluded from the analysis leaving all further results presented as n=8.

Analysis of food diaries revealed that baseline mean (95% CI) values for intake of energy, protein, fat and carbohydrate were 8228kj (7349.5 to 9106.4), 83.2g (67.6 to 98.8), 72.0g (57.5 to 86.5) and 218.7g (183.9 to 253.4) respectively. Repeated measures ANOVA with a Bonferroni adjustment indicated no significant differences (p=0.56) across the intervention days.

The (n=8) participants characteristics are presented in Table 1. Briefly, these participants had mean blood pressures within the normal range, lipid profiles were normal and glycaemic control (HbA1c) was excellent. Included male participants had a mean total body fat of 27.9%

with a mean of 21.5kg of fat mass and 55.7kg of fat free mass while female participants had a mean total body fat of 35.4%, a mean fat mass of 25.7kg and a mean fat free mass of 44.7kg, as determined through DXA. The mean glucose and insulin response (area under the curve) to the baseline OGTT and baseline insulin sensitivity estimated through OGIS index is presented in Table 1.

Based on our previously identified clinically important values which we determined by measuring the response to repeated, consecutive daily OGTT's (Gordon, et al., unpublished data, values shown below), we observed a potentially unfavourable and clinically meaningful increase in the insulin response on each of the four days following the resistance exercise session (>7,237 pmol.L^{-1}.120min^{-1}; Figure 2). A potentially unfavourable and clinically meaningful increase in the glucose response was also observed on the third day following exercise (>81 mmol.L^{-1}.120min^{-1}; Figure 3). No clinically meaningful change to OGIS index (>52 ml.min^{-1}.m^{-2}; Figure 4) was observed.

Discussion

The major finding from this study was insulin sensitivity may be adversely affected for up to four days following a single unaccustomed resistance exercise session. This is in contrast to previous findings of improved insulin sensitivity following a single bout of resistance exercise in young healthy untrained individuals (12, 13), young strength trained individuals (20), and older individuals with type 2 diabetes (11, 12). However, our results do concur with those that have shown no improvements to insulin sensitivity following an acute bout of resistance exercise (8-10). However, studies that have reported beneficial changes have generally involved individuals with poor glycaemic control, which may highlight the inability to improve something that is already functioning adequately (21).

Our current findings tend to suggest that a single session of unaccustomed resistance exercise may actually result in increased insulin production to maintain glucose homeostasis, or being

in a previously theorised state of transient insulin resistance (22). It is therefore important to look at mechanisms for why this may occur as a previous study of acute aerobic exercise in trained older individuals reported a beneficial increase to insulin sensitivity, for three but not five days (23) in comparison to our sedentary individuals who completed resistance exercise. This may suggest that it is necessary for people who already have good glycaemic control, to undertake a period of regular ongoing training to enable the working muscles to become responsive to the exercise stimulus and observe beneficial improvements to insulin sensitivity that have been shown following regular resistance training (24).

While we have excluded two individuals with hyperinsulinaemia from our analysis of healthy individuals, their individual results were noteworthy. The individual with extreme hyperinsulinaemia (insulin$\geq$200 pmol.L^{-1}) appeared to experience large beneficial increases in insulin sensitivity while the individual with a lower level of hyperinsulinaemia (130<insulin<200 pmol.L^{-1}) seemed to experience larger unfavourable reductions in insulin sensitivity. Therefore, we can cautiously suggest that these individuals with sub-optimal levels of metabolic health may respond differently and with greater magnitude. This however, requires further research in this specific population to elucidate why these differences may occur when compared to those individuals with insulin within the desirable range.

While considering the limitations of our study design with a small sample size, we can conclude that a single bout of resistance exercise does not improve insulin sensitivity in apparently healthy individuals with good glucose homeostasis and may indeed have a potentially adverse short-term effect. However, it may be that this study was underpowered and further research is required to confirm these results. We have identified potential issues for novice resistance training individuals to be aware of in the days immediately following resistance exercise. Further investigations into the training duration and frequency required before being able to observe known improvements to insulin sensitivity that occur from ongoing resistance training (24) are warranted. In addition, investigating the effect of a single

session of resistance exercise in individuals at risk of, or with type 2 diabetes is pertinent. Our current results pose further questions relating to the ability of ongoing resistance training to diminish the potentially adverse effects of acute resistance exercise and if this is the case, the length of time that training needs to occur for this to happen.

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Table 1: Participant Demographics

Outcome Measure	Mean (SD)
Male / Female	2 / 6
Age (years)	51.5 (6.3)
Weight (kg)	74.1 (11.2)
Height (cm)	170.1 (4.5)
BMI ($kg.m^{-2}$)	25.7 (4.2)
Waist:Hip	0.83 (0.07)
SBP (mm Hg)	122 (13)
DBP (mm Hg)	73 (10)
Cholesterol (mmol/L)	5.0 (1.0)
LDL (mmol/L)	2.9 (0.4)
HDL (mmol/L)	1.54 (0.53)
Triglycerides (mmol/L)	1.2 (1.0)
HbA1c (%)	5.5 (0.2)
Glucose (mmol/L)	4.9 (0.5)
Insulin (pmol/L)	73.3 (43.1)
$MET\text{-}mins.wk^{-1}$	968 (1053)
Sedentary Time (mins)	368 (126)
Bench Press 1RM (kg)	35.3 (13.1)
Leg Press 1RM (kg)	115.6 (27.2)
Shoulder Press 1RM (kg)	24.1 (9.2)
Calf Raise 1RM (kg)	225.6 (70.7)
Lat Pull-down 1RM (kg)	27.5 (10.0)
Glucose AUC ($mmol.L^{-1}.120mins^{-1}$)	762.2 (185.9)

Insulin AUC ($pmol.L^{-1}.120mins^{-1}$)	50,634.5 (26,128.7)
OGIS index ($ml.min^{-1}.m^{-2}$)	439.3 (82.7)

Data excludes that from the individuals with hyperinsulinaemia. BMI = body mass index; DBP = diastolic blood pressure; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MET = metabolic equivalents; SBP = systolic blood pressure; AUC = area under the curve.

Figure Legends:

Figure 1: Study protocol.

BP = blood pressure; IPAQ = international physical activity questionnaire; OGTT = oral glucose tolerance test; DXA = dual x-ray absorptiometry

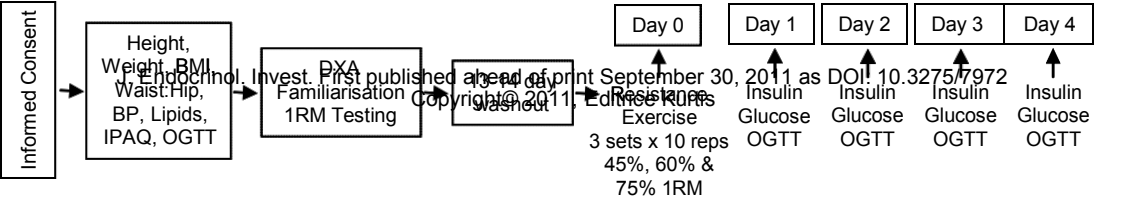
Figure 2: Change from baseline of insulin response (AUC) following exercise. Mean and 95% CI for eight included participants. Broken line represents the cut-point for a clinically meaningful change (>7237 $pmol.L^{-1}.120min^{-1}$).

Figure 3: Change from baseline of glucose response (AUC) following exercise. Mean and 95% CI for eight included participants. Broken line represents the cut-point for a clinically meaningful change (>81 $mmol.L^{-1}.120min^{-1}$).

Figure 4: Change from baseline of OGIS index following exercise. Mean and 95% CI for eight included participants. Broken line represents the cut-point for a clinically meaningful change (>52 $ml.min^{-1}.m^{-2}$).

J. Endocrinol. Invest. First published ahead of print September 30, 2011 as DOI: 10.3275/7972

Figure 1: Study protocol.
BP = blood pressure; IPAQ = international physical activity questionnaire; OGTT = oral glucose tolerance test; DXA = dual x-ray absorptiometry
31x6mm (150 x 150 DPI)



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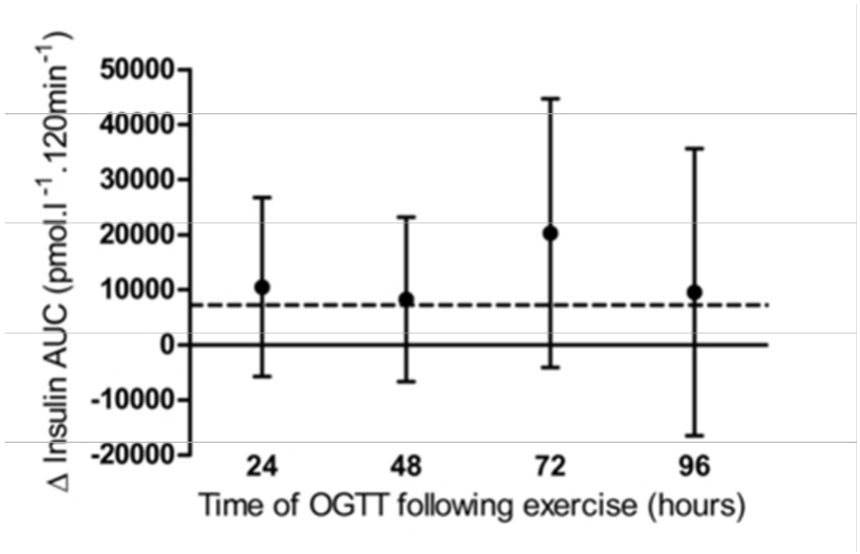

Figure 2: Change from baseline of insulin response (AUC) following exercise. Mean and 95% CI for eight included participants. Broken line represents the cut-point for a clinically meaningful change (>7237 pmol.L-1.120min-1).
71x46mm (150 x 150 DPI)

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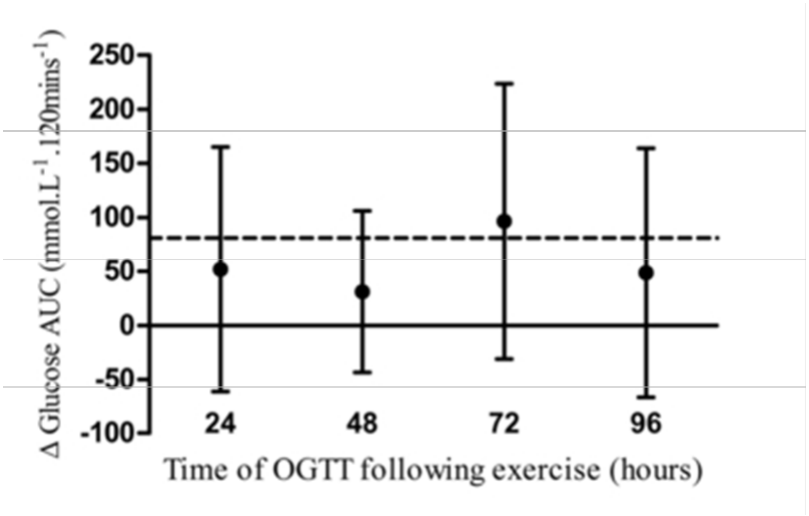

Figure 3: Change from baseline of glucose response (AUC) following exercise. Mean and 95% CI for eight included participants. Broken line represents the cut-point for a clinically meaningful change (>81 mmol.L-1.120min-1).
67x43mm (150 x 150 DPI)

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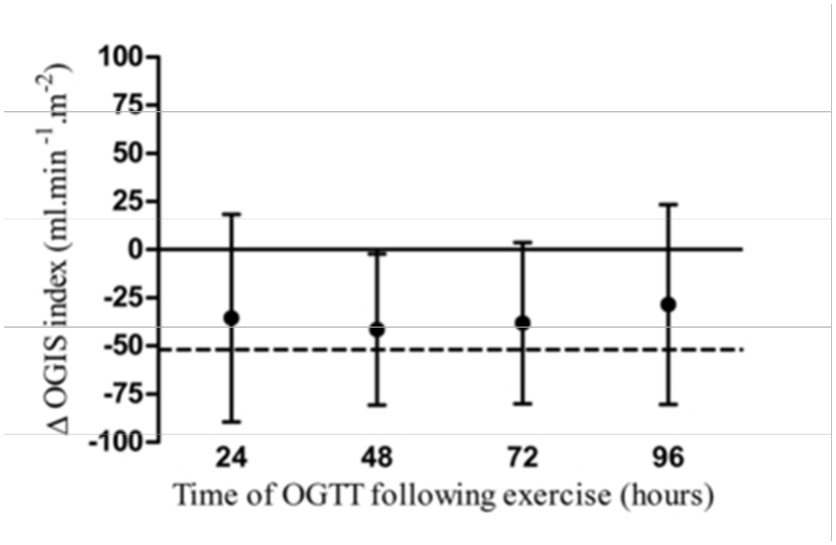

Figure 4: Change from baseline of OGIS index following exercise. Mean and 95% CI for eight included participants. Broken line represents the cut-point for a clinically meaningful change (>52 ml.min-1.m-2).
69x45mm (150 x 150 DPI)

Appendix B

Peer Reviewed Scientific Conference Presentations

Oral Presentations

Abstract presented at RMIT University's Higher Degree by Research student conference 2010

Presentation Title: Leptin and adiponectin responses to a single session of resistance exercise

Name: Mr Brett Gordon

School: Medical Sciences

Introduction: Health conditions such as obesity, insulin resistance and type 2 diabetes are associated with low grade inflammation. As the prevalence of these conditions continues to rise, interventions that result in reductions of adipose derived hormones should therefore be investigated to try to prevent or delay the disease progression.

Statement of Problem/Aim: Leptin and adiponectin are two adipocytokines that are used to measure inflammation and have been shown to respond to exercise. However, only one study to date has looked at the leptin response, and no studies have investigated the adiponectin response to a single resistance exercise session. Furthermore, research investigating the exercise response of these adipocytokines in people with type 2 diabetes is particularly lacking. Therefore the aim of this project was to investigate the responses of leptin and adiponectin in apparently healthy individuals and those with type 2 diabetes.

Outcomes: Apparently healthy individuals (n=10) and people with type 2 diabetes (n=10) completed a single session of resistance exercise and fasting blood tests on the three days following the exercise. On average, the people with diabetes were older and weighed more ($p<0.05$) however, their total and low-density lipoprotein cholesterol was lower ($p<0.05$). As expected, fasting glucose and glycated haemoglobin were higher ($p<0.05$) in those with diabetes. Following the resistance exercise session, repeated measures ANOVA showed no statistically significant change from baseline in either leptin (16.7ng/ml 95% CI: -40.3 to 73.6) or adiponectin (-0.7μg/ml 95% CI: -2.0 to 0.7) at any time from 24 to 72 hours after the exercise. This tends to indicate that in a previously sedentary population of people with and without type 2 diabetes, a single session of moderate to high intensity resistance exercise has no lasting effect on leptin or adiponectin and suggests that further research into the frequency of resistance exercise is required.

Gordon BA, Fraser SF, Bird SR, Benson AC. (2010). Leptin and adiponectin responses to a single session of resistance exercise. Oral presentation at Higher Degree by Research Student Conference - Presenting Tomorrow's Knowledge, RMIT University, Melbourne, Australia, 20 October 2010.

Abstract presented at RMIT University's Higher Degree by Research student conference 2011

Presentation Title: **A single session of resistance exercise does not modulate insulin sensitivity or adipocytokine markers of inflammation in individuals with and without type 2 diabetes.**

Name: Mr Brett Gordon

School: Medical Sciences

Introduction: Type 2 diabetes (T2D) is a condition of chronic insulin resistance that is linked to conditions of overweight and obesity, which are associated with low-grade inflammation. Exercise is recommended to prevent and treat T2D and has also been shown to improve adipocytokine markers of inflammation. However, compliance to exercise recommendations is poor in both individuals with and without T2D, although resistance exercise has been theorised to be more achievable than aerobic based exercise.

Statement of Problem/Aims: We sought to investigate the insulin sensitivity and inflammatory cytokine response in the three days following a single session of moderate-high intensity resistance exercise in middle-aged adults with and without T2D.

Outcomes: Ten apparently healthy individuals (males=3; females=7) and 10 individuals with T2D (males=6; females=4) with a mean (SD) age of 51.6 (5.8) years and 61.8 (7.2) years respectively, consented to participate. The individuals with T2D were older, weighed more, had impaired glycaemic control (higher HbA1c) and were less sensitive to insulin than the apparently healthy individuals ($p<0.05$). Repeated measures ANOVA failed to detect any group by time interactions for glucose, insulin, insulin sensitivity or insulin resistance ($p=0.63$), however a significant difference between groups for insulin sensitivity was abolished 48 hours after the resistance exercise session. There was no difference in adipocytokine markers of inflammation (adiponectin, leptin, interleukin-6, tumour necrosis factor alpha) prior to the resistance exercise session between groups ($p>0.05$), and we failed to detect any change 24 hours after the resistance exercise session (repeated measures ANOVA: $p=0.44$). These findings suggest that insulin sensitivity is not impacted by a single session of resistance exercise in middle-aged adults with and without T2D and that this is not caused by a change in adipocytokine markers of inflammation.

Gordon BA, Fraser SF, Bird SR, Benson AC. (2011). A single session of resistance exercise does not modulate insulin sensitivity or adipocytokine markers of inflammation in individuals with and without type 2 diabetes. Oral presentation at Higher Degree by Research Student Conference – Vision to Reality, RMIT University, Melbourne, Australia, 21 October 2011.

Abstract presented at Exercise and Sports Science Australia bi-annual conference in 2012

Continuous glucose response to resistance and aerobic exercise is similarly impaired in individuals with insulin requiring type 2 diabetes

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Introduction
Long-term resistance and aerobic exercise is known to improve glycaemic control and metabolic health[5]. Low intensity aerobic exercise[3] and combined resistance and aerobic exercise[4] have been reported to reduce the amount of time spent in hyperglycaemia. However, the continuous glucose response to acute resistance exercise in untrained individuals with type 2 diabetes (T2D) treated with insulin is not known. Further, it is unclear whether the response to acute resistance exercise is similar to that experienced with aerobic exercise.

Methods
Eight males with insulin treated T2D had their anthropometric, health and exercise capacity measured. Glucose levels were then monitored using the Medtronic iPro™2 continuous glucose monitoring system throughout the 24hrs prior to a single session of whole-body resistance exercise (3 sets, 10 repetitions at 70% one-repetition maximum) and 30 minutes of aerobic exercise (cycling at 60% VO_{2peak}), and for 3-days following each exercise session. The protocol was approved by the relevant Human Research Ethics Committees and participants provided informed consent prior to their involvement in this randomised cross-over trial where each individual completed each mode of exercise seven days apart. Regular insulin and medication doses were maintained except for immediately before exercise where half the prescribed insulin dose was administered. Data were analysed using repeated measures ANOVA.

Results
Participants mean (SD) age was 61.0 (7.2) years, were diagnosed with T2D 18.0 (8.5) years ago, weighed 102.8 (35.4) kg with HbA1c of 8.0% (0.3)%. During the 24hrs pre-exercise intervention, participants experienced blood glucose ≥10mmol.L^{-1} (hyperglycaemia) for 25.0% and 24.5% of the day prior to resistance and aerobic exercise respectively. We failed to detect a significant intervention by time interaction, however a trend for a time effect (p=0.06) was found with pair-wise comparison revealing a significant increase (p=0.05) in hyperglycaemia in the 24hrs after completing a single session of exercise. We also found a time effect (p=0.03) for continuous glucose response, with a significant increase (p=0.002) from the 24hrs pre-exercise to the immediate 24hrs post-exercise.

Conclusion
In novice exercisers, glycaemic control, when measured continuously, appears to be impaired to a similar extent following a single session of both resistance and aerobic exercise. These findings differ from those reported after a single session of aerobic exercise[3], low-intensity resistance exercise combined with short high-intensity aerobic exercise[4], or resistance exercise[1] (measured by oral glucose tolerance testing) and may be due to a suggested transient insulin resistance[2]. Whilst chronic

exercise participation has been shown to improve glucose tolerance and control, regular sessions of exercise may be required to overcome the apparent transient impaired glycaemic control.

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5. Snowling, NJ. & Hopkins WG. *Diabetes Care* 2006;29(11):2518-2527

Gordon BA, Bird SR, MacIsaac RJ, Benson AC. (2012). Continuous glucose response to resistance and aerobic exercise is similarly impaired in individuals with insulin requiring type 2 diabetes. Oral presentation at ESSA conference, Gold Coast, Australia, 19-21 April 2012

Appendix C

Peer Reviewed Scientific Conference Presentations

Poster Presentations

Abstract presented at Australian Diabetes Society meeting in 2009

A 4-day Time Course for Insulin Sensitivity in Response to a Single Bout of Resistance Exercise in Healthy 40-60 Year Olds

Gordon, Brett[1], Fraser, Steve[2], Bird, Stephen[1], Benson**,** Amanda[1]
[1] Exercise Metabolism Group, School of Medical Sciences, RMIT University, Melbourne, Victoria, Australia; [2] School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Victoria, Australia

Introduction
Insulin sensitivity has been measured in response to a single acute bout of resistance exercise in previously healthy individuals[1-5], but the response has not been tracked for longer than 36-hours[3]. Therefore, the purpose of this study was to track the effect of an acute bout of resistance exercise on insulin sensitivity over 96-hours, in the context of exercise prescription recommendations.

Methods
Ten sedentary (completing less than 20-minutes of aerobic exercise twice weekly), non-diabetic males (N=3) and females (N=7) with a mean age of 51.6 (5.78) years consented to participate after ethical approval. Baseline testing consisted of height, weight, lipid profile, oral glucose tolerance test (OGTT) and one-repetition maximum strength testing. After a 2-week wash-out, participants underwent a single resistance exercise session before returning on each of the subsequent 4-days to undergo OGTT's.

Results
Sixty percent of participants were overweight (40%) or obese (20%) with mean BMI = 25.8 (4.4) kg/m^2. Participants had normal lipid profiles and good glycaemic control (HbA1c$\leq$6.1); mean fasting glucose = 4.9 (0.5) mmol/l and insulin = 95.6 (84.9) pmol/l, although two individuals appeared to be hyperinsulinaemic (>167 pmol/l). Resistance exercise resulted in no statistically significant changes in insulin sensitivity. However, individual variances may explain this lack of change, with four participants more insulin sensitive 24-hours following exercise according to the oral glucose insulin sensitivity (OGIS) index, with two of these remaining increased at 96-hours. Two individuals also experienced increased insulin sensitivity at 96-hours despite some initial insulin resistance. Similar trends were observed for both OGIS and area under the insulin and glucose curves.

Conclusion
This data indicates variations in individual responses and that further investigation is warranted to determine the most effective exercise prescription for metabolic health. Whether a similar response is seen in individuals with type 2 diabetes is yet to be fully investigated.

References
1. Andersen, E. and A.T. Hostmark, *Effect of a single bout of resistance exercise on postprandial glucose and insulin response the next day in healthy, strength-trained men.* J Strength Cond Res, 2007. **21**(2):487-91.

2. Chapman, J., et al., *Unaltered insulin sensitivity after resistance exercise bout by postmenopausal women.* Med Sci Sports Exerc, 2002. **34**(6):936-41.
3. King, D.S., et al., *Effects of eccentric exercise on insulin secretion and action in humans.* J Appl Physiol, 1993. **75**(5):2151-6.
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5. Luebbers, P.E., et al., *Glucose uptake after resistance training of different intensities but of equal work volume.* J Strength Cond Res, 2008. **22**(4):1094-100.

Gordon BA, Fraser SF, Bird SR, Benson AC. (2009). A 4-day time course for insulin sensitivity in response to a single bout of resistance exercise in healthy 40-60 year olds. Poster presentation at 2009 ADS/ADEA Annual Scientific Meeting, Adelaide, Australia, 26-28 August 2009.

A 4-day Time Course for Insulin Sensitivity in Response to a Single Bout of Resistance Exercise in Healthy 40-60 Year Olds

B. A. Gordon[1], S. F. Fraser[2], S. R. Bird[1], A. C. Benson[1]

[1]Exercise Metabolism Group, School of Medical Sciences, RMIT University, Melbourne, Australia
[2]School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

Introduction

Resistance training has been the recent focus of a number of diabetes treatment and prevention studies, however there continues to be a lack of agreement in terms of the most effective dose. Insulin sensitivity has been measured in response to a single acute bout of resistance exercise in previously healthy individuals [1-5], but the response has not been tracked for longer than 36-hours [3]. Results from these studies are mixed, with some reporting improvements in insulin sensitivity and others refuting this effect. Therefore, the purpose of this study was to track the effect of an acute bout of resistance exercise on insulin sensitivity over 96-hours, in the context of exercise prescription recommendations [6-7].

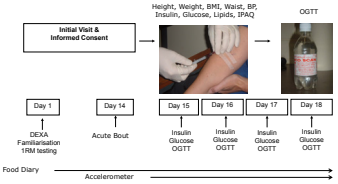
Hypothesis

A single bout of moderate to high intensity resistance exercise will improve insulin sensitivity for 48 hours following this bout.

Methodology

Study Design:

Ten sedentary (completing less than 20-minutes of aerobic exercise twice weekly), non-diabetic males (N=3) and females (N=7) with a mean age of 51.6 (5.8) years consented to participate after ethical approval. Baseline testing consisted of height, weight, lipid profile, oral glucose tolerance test (OGTT) and one-repetition maximum strength testing on five exercises. After a 2-week wash-out, participants underwent a single resistance exercise session before returning on each of the subsequent 4-days to undergo OGTT's.



Measurements:

Body Mass & Height, (c.v.=0.03% & 0.10%)
Body Mass Index (BMI) ***(Weight (kg) / Height^2(m))***

Waist Circumference (WC), (c.v.=0.19%)

Bloods (fasting lipids, HbA1c, glucose, insulin), (c.v.= TC=2%, HDL-C=9%, LDL-C=12%, TG=3.5%, HbA1c=3%, Glucose=1.1%, Insulin=12.1%)

Oral Glucose Insulin Sensitivity (OGIS) and Area Under the Curve (AUC). OGIS and AUC are mathematical modeling equations that are validated against the hyperinsulinemic glucose clamp to predict insulin sensitivity from an OGTT.

1RM testing:
A progressive protocol to failure on 2 consecutive attempts on the following exercises – bench press, 45˚ leg press, shoulder press, calf raises & lateral-pulldown.

Acute Resistance Exercise Bout:
The progressive exercise bout consisted of 3 sets of 10 repetitions for each exercise. Each set was completed at 45%, 60% & 75% of the participants 1RM for each exercise with 60 seconds recovery between sets. Stretches were completed as a cool-down. This exercise bout took approximately 50 minutes to complete.

Statistical Analysis:

- All data were analysed using SPSS version 15 for Windows with significance set at an alpha level of p<0.05.
- A one-way repeated measures analysis of variance (ANOVA) was completed to assess the change over time for insulin sensitivity.
- Data are presented as means ± standard deviation (SD) unless otherwise indicated.

Results

Participant demographics can be seen in Table 1 and shows that participants had normal lipid profiles and good glycaemic control, although two individuals appeared to be hyperinsulinaemic (>167 pmol/l). Sixty percent of participants were overweight (40%) or obese (20%) with mean BMI = 25.8 (4.4) kg/m^2. Participants non-diabetic status was endorsed during the baseline OGTT and 2-hour plasma glucose measurement.

Table 1: Participant Demographics

Outcome	Mean (SD)
N	10
Male / female	3 / 7
Age (years)	51.6 (5.8)
Height (cm)	170.8 (7.9)
Weight (kg)	74.7 (10.0)
SBP (mmHg)	118 (13)
DBP (mmHg)	73 (9)
TC (mmol/l)	5.1 (0.8)
LDL-C (mmol/l)	3.0 (0.4)
HDL-C (mmol/l)	1.53 (0.47)
TG (mmol/l)	1.2 (0.9)
HbA1c (%)	5.6 (0.3)
Fasting Glucose (mmol/l)	4.9 (0.5)
2-hr Plasma Glucose (mmol/l)	5.3 (1.6)
Fasting Insulin (pmol/l)	95.6 (84.9)
MET-mins/wk (IPAQ)	987 (931.1)
Sitting Time (mins/wk, IPAQ)	378 (141.5)

A single bout of resistance exercise resulted in no statistically significant changes in insulin sensitivity at any point in time (Figures 1a & 1b). It is interesting to note though, that there was less variance for the area under the insulin curve and also Oral Glucose Insulin Sensitivity (OGIS) index at 48 hours following the exercise bout, suggesting that some of the participants at least experienced improved insulin sensitivity following resistance exercise.

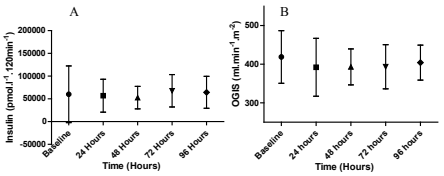


Figure 1: Area Under the Insulin Curve across days (A); OGIS across days (B); Mean & 95% CI.

Individual variances may explain this lack of change, with four participants more sensitive to insulin 24-hours following exercise according to the OGIS index, with two of these remaining increased at 96-hours. Two individuals also experienced increased insulin sensitivity at 96-hours despite some initial insulin resistance. Similar trends were observed for both OGIS and area under the insulin curves (Figures 2a & 2b).

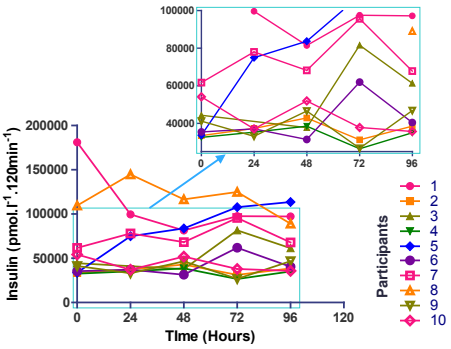


Figure 2a: Individual Responses for Insulin AUC across days.

Results cont.

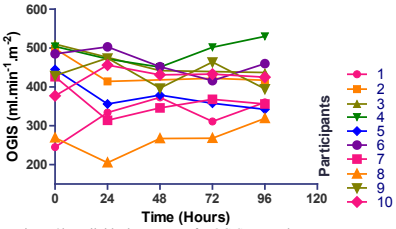


Figure 2b: Individual Responses for OGIS across days.

The results tend to suggest that individuals completing a bout of unfamiliar resistance exercise may result in a period of transient insulin resistance, a phenomenon that has been suggested previously to be associated with a state of increased inflammation [8]. Therefore, future studies should also investigate markers of inflammation to be able to further investigate this possibility.

Conclusions

- There is individual variation in the way that individuals respond to a single bout of unfamiliar resistance exercise with improvements in insulin sensitivity occurring at different time points.
- This study investigated apparently healthy individuals and it remains to be seen if individuals with type 2 diabetes respond in the same way over this time course after a single bout of resistance exercise.

Where to From Here?

- **Investigate the effect of an unfamiliar bout of resistance exercise on markers of inflammation and transient insulin resistance.**
- **Investigate whether individuals with type 2 diabetes respond differently to apparently healthy individuals.**
- **Investigate whether this response changes in individuals who regularly participate in resistance training exercise.**
- **The results of this study warrant further investigation to determine the most effective exercise prescription for metabolic health.**

Acknowledgments

We would like to gratefully acknowledge the efforts and commitment of all of the participants involved in the study.

BAppSci (Human Movement), RMIT University, students for their valuable assistance with testing and training.

Brett Gordon is supported by a RMIT, School of Medical Sciences research scholarship.

References

1. Andersen, E. and A.T. Hostmark, *Effect of a single bout of resistance exercise on postprandial glucose and insulin response the next day in healthy, strength-trained men.* J Strength Cond Res, 2007. 21(2): p. 487-91.
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3. King, D.S., et al., *Effects of eccentric exercise on insulin secretion and action in humans.* J Appl Physiol, 1993. 75(5): p. 2151-6.
4. Fluckey, J.D., et al., *Effects of resistance exercise on glucose tolerance in normal and glucose-intolerant subjects.* J Appl Physiol, 1994. 77(3): p. 1087-92.
5. Luebbers, P.E., et al., *Glucose uptake after resistance training of different intensities but of equal work volume.* J Strength Cond Res, 2008. 22(4): p. 1094-100.
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Abstract presented at RMIT University's Higher Degree by Research student conference 2009

The insulin response following a single bout of resistance exercise varies between healthy individuals and those with type 2 diabetes.

[1]Brett A Gordon, [2]Steve F Fraser, [1]Stephen R Bird, [1]Amanda C Benson
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Type 2 diabetes is a major health epidemic, affecting between 7-10% of the Australian population. Lifestyle modifications, including exercise and healthy eating, are recommended as the first line of treatment, with clear guidelines developed for aerobic type exercise such as walking. However, due to the numerous co-morbidities generally associated with type 2 diabetes, it can be difficult to attain these recommendations. Therefore, resistance training presents a viable and more tolerable option, however further development of current guidelines is needed for this cohort.

The aim of this study was to determine the length of time that improvements to insulin sensitivity and glucose transport remained following a single acute bout of resistance exercise; to determine the most effective frequency of resistance training. Fasting blood samples were collected for this prior to undergoing the resistance training bout and for the following three days, with homeostasis modelling assessment (HOMA) equations used to determine insulin sensitivity and resistance.

To our knowledge, this is the first study that has tracked the insulin response following a single resistance exercise bout for greater than 24-hours and 36–hours in people with and without type 2 diabetes respectively. The initial insulin sensitivity response (24-hours post training) appears relatively unchanged in individuals with type 2 diabetes, while tending to decrease in individuals without type 2 diabetes. At 48-hours, there is a similar response in both individuals with and without type 2 diabetes. However, the 72-hour response appears to track in opposite directions with a tendency for individuals with type 2 diabetes to increase their insulin sensitivity. This new information will be important in developing resistance training guidelines, as it shows that while the early response to acute resistance exercise is similar between individuals with and without type 2 diabetes, there are differences that should also be considered for exercise prescription.

Gordon BA, Fraser SF, Bird SR, Benson AC. (2009). The insulin response following a single bout of resistance exercise varies between individuals with and without type 2 diabetes. Poster presentation at A Step Ahead: Higher Degrees by Research Student Conference 2009, RMIT University, Melbourne, Australia, 23 October 2009.

The insulin response following a single bout of resistance exercise varies between individuals with and without type 2 diabetes

B. A. Gordon[1], S. F. Fraser[2], S. R. Bird[1], A. C. Benson[1]

[1]Exercise Metabolism Group, School of Medical Sciences, RMIT University, Melbourne, Australia

[2]School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

Introduction

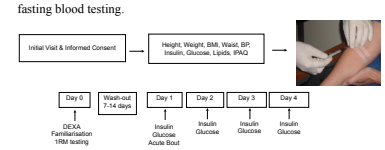
Resistance training has been the recent focus of a number of diabetes treatment and prevention studies, however there continues to be a lack of agreement in terms of the most effective dose. Insulin sensitivity has been measured in response to a single acute bout of resistance exercise in previously healthy individuals [1-5] and people with type 2 diabetes [4, 6], but the response has not been tracked for longer than 36-hours in people without type 2 diabetes and 24 hours in those with type 2 diabetes. Results from studies involving individuals without type 2 diabetes are mixed, with some reporting improvements in insulin sensitivity and others refuting this effect. However, the effect of resistance exercise appears to be more definitive in people with type 2 diabetes with both [4, 6] studies reporting improvements in insulin sensitivity. The aim of this study was to determine the length of time that improvements to insulin sensitivity and glucose transport remained following a single acute bout of resistance exercise; to determine the most effective frequency of resistance training.

Hypothesis

A single bout of moderate to high intensity resistance exercise will improve insulin sensitivity following this bout for 48 hours in people with type 2 diabetes compared with no change in people without type 2 diabetes.

Methodology

Study Design:
Ten sedentary (completing less than 20-minutes of aerobic exercise twice weekly), individuals without type 2 diabetes and 10 sedentary individuals with type 2 diabetes consented to participate after ethical approval. Baseline testing consisted of height, weight, lipid profile, fasting glucose and insulin, international physical activity questionnaire (IPAQ) and one-repetition maximum (1RM) strength testing on five exercises. After a 7-14 day washout period, participants underwent a single resistance exercise session before returning on each of the subsequent three days to undergo fasting blood testing.



Measurements:

Body Mass & Height: (c.v.=0.3% & 0.10%)
Body Mass Index (BMI) – *(Weight (kg) / Height^2 (m))*

Waist Circumference (WC): (c.v.=0.19%)

Bloods (fasting lipids, HbA1c, glucose, insulin: (c.v.= TC=2%, HDL-C=9%, LDL-C=12%, TG=3.5%, HbA1c=3%, Glucose=1%, Insulin=12.1%)

1RM Testing:
A progressive protocol to failure on two consecutive attempts on the following exercise – bench press, 45° leg press, shoulder press, calf raises & lateral-pulldown.

Acute Resistance Exercise Bout:
The progressive exercise bout consisted of 3 sets of 10 repetitions for each exercise. Each set was completed at 45%, 60% and 75% of the participants 1RM for each exercise with 60 seconds recovery between sets. Stretches were completed as a cool-down. This exercise bout took approximately 50 minutes to complete.

Statistical Analysis:
- Data are presented as mean (standard deviation), unless otherwise indicated.
- A two-way repeated measures (group x time) analysis of variance (ANOVA) was completed to assess the change over time for insulin sensitivity, with independent T tests comparing groups at individual time points.
- All data were analysed using SPSS version 17 for Windows with significance set at an alpha level of p<0.05.

Results

Participant demographics can be seen in Table 1 and shows that participants had normal lipid profiles and good glycaemic control, although two individuals without type 2 diabetes and four individuals with type 2 diabetes appeared to be hyperinsulinaemic (>150 pmol/l). Sixty percent of the participants without type 2 diabetes were overweight (40%) or obese (20%) with mean BMI = 25.8 (4.4) kg/m^2 while 90% of people with type 2 diabetes were overweight (50%) or obese (40%) with mean BMI = 29.6 (3.9) kg/m^2.

Table 1: Participant Demographics

Outcome	Type 2 Diabetes	No Diabetes
N	10	10
Male / female	6/4	3 / 7
Age (years)	61.8 (7.2)	51.6 (5.8)
Height (cm)	169.7 (7.7)	170.8 (7.9)
Weight (kg)	86.8 (13.4)	74.7 (10.0)
Duration of Diabetes (years)	8.3 (5.1)	N/A
SBP (mmHg)	131 (20)	118 (13)
DBP (mmHg)	74 (8)	73 (9)
TC (mmol/l)	4.1 (0.6)	5.1 (0.8)
LDL-C (mmol/l)	2.1 (0.4)	3.0 (0.4)
HDL-C (mmol/l)	1.32 (0.22)	1.53 (0.47)
TG (mmol/l)	1.6 (0.6)	1.2 (0.9)
HbA1c (%)	6.8 (0.6)	5.6 (0.3)
Fasting Glucose (mmol/l)	7.6 (1.6)	4.9 (0.5)
Fasting Insulin (pmol/l)	137.9 (82.5)	95 (84.9)
MET-mins/wk (IPAQ)	501 (273.4)	987 (931.1)
Sitting Time (mins/wk, IPAQ)	467 (209.5)	378 (141.5)

Results cont.

As might be expected, there was a significant difference for fasting glucose levels between groups (p<0.01) and the mean insulin sensitivity was higher in the individuals without type 2 diabetes at all time points, but only statistically significant at time point zero (Figure 1). There were no within group differences found over time for either group in regards to fasting glucose, insulin or insulin sensitivity estimated using the Homeostasis Modelling Assessment (HOMA) equation. Individual variation in insulin sensitivity in response to a single resistance exercise bout is shown in figures 2 and 3 and indicates that while many of the participants had a similar response to the resistance exercise, some individuals responded differently and require further investigation.

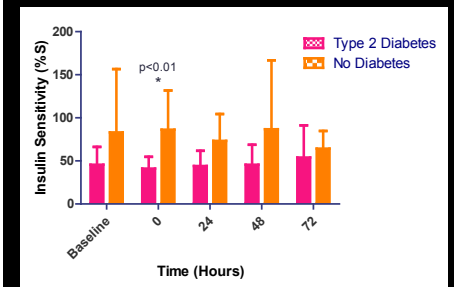


Figure 1: Mean insulin sensitivity (HOMA) before and after resistance exercise.

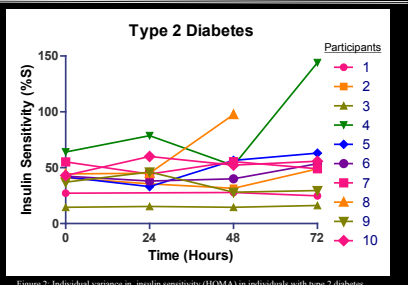


Figure 2: Individual variance in insulin sensitivity (HOMA) in individuals with type 2 diabetes.

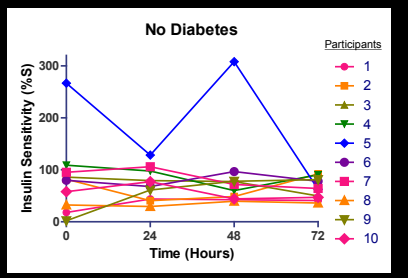


Figure 3: Individual variance in insulin sensitivity (HOMA) in individuals without type 2 diabetes.

Conclusion

- To our knowledge, this is the first study that has tracked the insulin response following a single resistance exercise bout for greater than 24-hours and 36–hours in people with and without type 2 diabetes respectively.
- There appears to be no change in insulin sensitivity following a single bout of resistance exercise in previously sedentary individuals with and without type 2 diabetes. This is in contrast to previous literature in individuals with type 2 diabetes [4, 6] that suggest an improvement to insulin sensitivity following a single bout of resistance exercise. This suggests further research is required to examine the effect of exercise intensity, type or the potential for change in each participant.

Where to Next?

- **Investigate the effect of an unfamiliar bout of resistance exercise on markers of inflammation and transient insulin resistance.**
- **Investigate whether participation in a regular resistance exercise program changes this response.**

Acknowledgements

We would like to gratefully acknowledge the efforts and commitment of all of the participants involved in the study.

BAppSci (Human Movement), RMIT University, students for their valuable assistance with testing and training.

Brett Gordon is supported by a RMIT, School of Medical Sciences research scholarship.

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1. Andersen, E. and A.T. Hostmark, *Effect of a single bout of resistance exercise on postprandial glucose and insulin response the next day in healthy, strength-trained men.* J Strength Cond Res, 2007. 21(2): p. 487-91.
2. Chapman, J., et al., *Unaltered insulin sensitivity after resistance exercise bout by postmenopausal women.* Med Sci Sports Exerc, 2002. 34(6): p. 936-41.
3. King, D.S., et al., *Effects of eccentric exercise on insulin secretion and action in humans.* J Appl Physiol, 1993. 75(5): p. 2151-6.
4. Fluckey, J.D., et al., *Effects of resistance exercise on glucose tolerance in normal and glucose-intolerant subjects.* J Appl Physiol, 1994. 77(3): p. 1087-92.
5. Luebbers, P.E., et al., *Glucose uptake after resistance training of different intensities but of equal work volume.* J Strength Cond Res, 2008. 22(4): p. 1094-100.
6. Fenicchia, L.M., et al., *Influence of resistance exercise training on glucose control in women with type 2 diabetes.* Metabolism, 2004. 53(3): p. 284-9.

Abstract presented at Exercise and Sports Science Australia bi-annual conference in 2010

Consecutive oral glucose tolerance testing with or without prior resistance training does not affect insulin sensitivity in apparently healthy adults.

Gordon, Brett A.[1], Fraser, Steve F.[2], Bird, Stephen R.[1], Benson, Amanda C.[1]
[1]RMIT University, Melbourne, Australia.
[2]Deakin University, Melbourne, Australia.

Introduction: Insulin sensitivity is a key component of type 2 diabetes (T2D) that decreases as the disease progresses. The oral glucose tolerance test (OGTT) is used to diagnose T2D and frequently to estimate insulin sensitivity; however, the effect of repeated, daily OGTT's is unclear. Therefore, the purpose of this study was to track the insulin sensitivity response to four-consecutive OGTT's and assess the impact of a prior single resistance exercise bout.

Methods: RMIT University human research ethics committee approved the study and all participants gave informed consent. Twenty sedentary, apparently healthy individuals were recruited with ten (51.6±5.8 years) completing a single resistance exercise (RE) bout followed by four OGTTs on consecutive days and ten (54.6±6.5 years) completing four OGTTs on consecutive days without a prior resistance exercise bout (No-RE).

Results: At baseline, there was a significant difference in insulin sensitivity between groups according to the oral glucose insulin sensitivity index (418.8±95.1ml.min^{-1}.m^{-2}, RE; 333.6±71.9ml.min^{-1}.m^{-2}, No-RE; p=0.04), however this difference was not present at any other time. There was no change in insulin sensitivity following repeated multiple OGTT's, in either the RE or No-RE groups at any time point.

Conclusion: Repeated OGTT's provide a reliable estimate of insulin sensitivity in apparently healthy individuals that does not appear to be affected by administration on consecutive days. Additionally, a single moderate-high intensity resistance exercise bout did not produce a discernable change in insulin sensitivity. The number of resistance exercise sessions required before changes to insulin sensitivity can be detected requires further investigation.

Gordon BA, Fraser SF, Bird SR, Benson AC. (2010) Consecutive oral glucose tolerance testing with or without prior resistance training does not affect insulin sensitivity in apparently healthy adults. Poster presentation at ESSA conference, Gold Coast, Australia, 9-11 April 2010

Consecutive oral glucose tolerance testing with or without prior resistance training does not affect insulin sensitivity in apparently healthy individuals

B. A. Gordon[1], S. F. Fraser[2], S. R. Bird[1], A. C. Benson[1]
[1]School of Medical Sciences, RMIT University, Melbourne, Australia
[2]School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

Introduction

- Insulin sensitivity is a key component of type 2 diabetes that worsens as the disease progresses.
- The oral glucose tolerance test (OGTT) is used to diagnose type 2 diabetes and frequently to estimate insulin sensitivity; however, the effect of repeated, daily OGTT's is unclear.
- In apparently healthy individuals, insulin sensitivity has been reported to increase 24 hours following a single session of resistance exercise [1] and insulin action has been reported to increase approximately 36 hours following unaccustomed eccentric resistance exercise [2].
- Other studies however, have reported impaired insulin action following a single bout of resistance training [3].
- The primary aim of this study was to assess the impact of consecutive OGTT's on insulin sensitivity. The secondary aim was then to determine if a single, acute bout of resistance exercise resulted in improved insulin sensitivity and glucose transport and how long any changes remained; to determine the most effective frequency of resistance training.

Hypothesis

- Repeated, daily OGTT's will not affect insulin sensitivity.
- Insulin Sensitivity will improve for 48 hours following a single bout of moderate to high intensity resistance exercise.

Methodology

Study Design:
Twenty sedentary (completing less than 20-minutes of aerobic exercise twice weekly), apparently healthy individuals consented to participate after ethical approval. Baseline testing consisted of height, weight, lipid profile, fasting glucose and insulin, OGTT, international physical activity questionnaire (IPAQ) and one-repetition maximum (1RM) strength testing on five exercises in the group undertaking the resistance exercise bout. The study protocol is outlined in Figure 1.

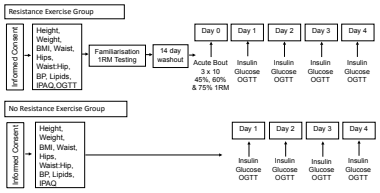


Figure 1: Study Protocol

Measurements:


Body Mass & Height: (c.v. = 0.3% & 0.10%)
Body Mass Index (BMI) – *(Weight (kg) / Height^2 (m))*


Waist Circumference (WC): (c.v. = 0.19%)


Bloods (fasting lipids, HbA1c, glucose, insulin: (c.v. = TC = 2%, HDL-C = 9%, LDL-C = 12%, TG = 3.5%, HbA1c = 3%, Glucose < 1%, Insulin = 8.45%)


1RM Testing:
A progressive protocol to failure on two consecutive attempts on the following exercises – bench press, 45° leg press, shoulder press, calf raises & lateral-pulldown.


Acute Resistance Exercise Bout:
The progressive exercise bout consisted of 3 sets of 10 repetitions for each exercise. Each set was completed at 45%, 60% and 75% of the participant's 1RM for each exercise with 60 seconds recovery between sets.


Oral Glucose Insulin Sensitivity (OGIS) and Area Under the Curve (AUC). OGIS and AUC are mathematical modeling equations that are validated against the euglycaemic hyperinsulinemic glucose clamp to predict insulin sensitivity from an OGTT.

Statistical Analysis:
- Data are presented as mean (standard deviation), unless otherwise indicated.
- A two-way, mixed-between, repeated measures (group x time) analysis of variance (ANOVA) was completed to assess the change over time for insulin sensitivity.
- All data were analysed using SPSS version 17 for Windows with significance set at an alpha level of $p<0.05$.

Results

Participant demographics can be seen in Table 1 and shows that participants had normal lipid profiles, blood pressure and good glycaemic control. The mean BMI for the resistance exercise group was 25.8 (4.5) kg/m^2 while it was 33.3 (6.3) kg/m^2 for the no resistance exercise group. One individual from the resistance exercise group and two from the no resistance exercise group had an abnormal response to the initial OGTT that would indicate they had impaired glucose tolerance. Two individuals from the resistance exercise group and four from the no resistance exercise group were hyperinsulinaemic (>130 pmol/L) at baseline.

Table 1: Participant Demographics

Measure	Resistance Exercise	No Resistance Exercise
Male / Female	3 / 7	3 / 7
Age (years)	51.6 (5.8)	54.6 (6.5)
Weight (kg)	74.7 (10.0)	93.4 (16.4)*
Height (cm)	170.8 (7.9)	167.7 (6.8)
BMI (kg.m^{-2})	25.8 (4.5)	33.3 (6.3)*
Waist:Hip	0.83 (0.07)	0.88 (0.08)
BP (mmHg)	120 (13) / 74 (9)	126 (14) / 83 (10)*
Cholesterol (mmol/L)	5.1 (0.8)	4.9 (1.2)
LDL (mmol/L)	3.0 (0.4)	2.8 (1.0)
HDL (mmol/L)	1.53 (0.47)	1.42 (0.24)
Triglycerides (mmol/L)	1.2 (0.9)	1.6 (0.5)
HbA1c (%)	5.6 (0.3)	5.5 (0.3)
Glucose (mmol/L)	4.9 (0.5)	5.4 (0.4)
Insulin (pmol/L)	95.6 (84.9)	129 (82.7)
MET-mins.wk^{-1} (IPAQ)	987 (931)	1428 (1365)
Sedentary Time (mins)	378 (142)	435 (207)

* = significantly different between groups ($p<0.05$). NB: only diastolic BP was different

Results cont.

- There was no change over time for area under the insulin curve for either group (Figure 2).
- The OGIS showed good reproducibility as there was no change over time for insulin sensitivity for either group (Figures 3 & 4).
- There was no change over time for 120 minute glucose levels for either group and no significant difference between groups (Figure 5).

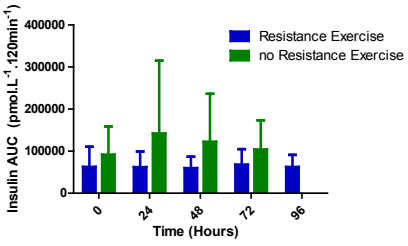


Figure 2: Mean (SD) area under the insulin curve for each OGTT.

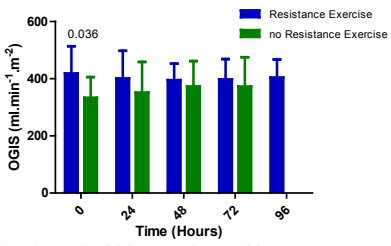


Figure 3: Mean (SD) OGIS calculated from each OGTT.

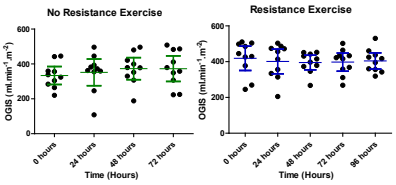


Figure 4: Variance in insulin sensitivity over time. Mean and 95% CI.

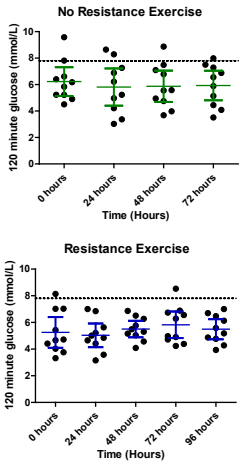


Figure 5: Variance in 120 minute glucose from the OGTT over time. Mean and 95% CI. Dotted line represents the cut off for a normal response.

Conclusion

- Repeated OGTT's provide a reliable estimate of insulin sensitivity in apparently healthy individuals that does not appear to be affected by administration on consecutive days.
- A single bout of moderate to high intensity resistance exercise did not produce a discernable change in insulin sensitivity.
- The OGTT produces moderately reproducible results in terms of glucose levels.

Where to Next?

- **Investigate the effect of an unfamiliar bout of resistance exercise on markers of inflammation and transient insulin resistance.**
- **Investigate the number of resistance exercise sessions required before changes to insulin sensitivity can be detected.**

Acknowledgements

We would like to gratefully acknowledge the efforts and commitment of all of the participants involved in the study.

BAppSci (Human Movement), RMIT University, students for their valuable assistance with testing and training.

Brett Gordon is supported by a RMIT, School of Medical Sciences research scholarship.

References

1. Koopman, R., et al., A single session of resistance exercise enhances insulin sensitivity for at least 24 hours in healthy men. Euro J App Physiol, 2005. 94(1-2): p. 180-187.
2. King, D.S., et al., *Effects of eccentric exercise on insulin secretion and action in humans.* J Appl Physiol, 1993. 75(5): p. 2151-2156
3. Howlett, KF., et al., Resistance exercise and insulin regulate AS160 and interaction with 14-3-3 in human skeletal muscle. Diabetes, 2007. 56(6): p. 1608-1614.

Abstract presented at Exercise and Sports Science Australia bi-annual conference in 2010

No change in insulin sensitivity following a single bout of resistance exercise in individuals with and without type 2 diabetes.

Gordon, Brett A[1], Fraser, Steve F[2], Bird, Stephen R[1], Benson, Amanda C[1]
[1]*RMIT University, Melbourne, Victoria, Australia*
[2]*Deakin University, Melbourne, Victoria, Australia*

Introduction: Type 2 diabetes (T2D) is a major health epidemic, affecting between 7-10% of all Australians. Aerobic exercise is recommended for T2D, but is difficult for some individuals to attain the required volume and intensity. Therefore, resistance training has been proposed as a viable and more tolerable option. The aim of this study was to determine the time-course of changes to insulin sensitivity following a single bout of resistance exercise.

Methods: RMIT University human research ethics committee approved this study and all participants gave written informed consent prior to participating. Ten apparently healthy (51.6±5.8 years) and 10 individuals with T2D (61.8±7.2 years) participated. Fasting blood samples were collected prior to undergoing a resistance exercise bout and on three subsequent days. Homeostasis modelling assessment (HOMA) equations were used to determine insulin sensitivity.

Results: Mean insulin sensitivity was greater in individuals without T2D, although was only significantly different immediately prior to (86.2±45.5%, apparently healthy; 41.1±13.6%, diabetes; p=0.01) and after (p=0.03) the resistance exercise bout. Following the resistance exercise bout, no change in insulin sensitivity was detected in either cohort.

Conclusion: A single resistance exercise bout produced no discernable change to insulin sensitivity in the majority of these participants. These findings are in contrast to previous literature[1] concerning acute resistance exercise in T2D and suggest further research is required to examine participant health status on the potential for change in insulin sensitivity and the time-course for any changes.

References

1. Fennichia, LM., Kanaley, JA., et al. 2004. *Metabolism: Clinical and Experimental.* 53;284-289

Gordon BA, Fraser SF, Bird SR, Benson AC. (2010) No change in insulin sensitivity following a single bout of resistance exercise in individuals with and without type 2 diabetes. Poster presentation at ESSA conference, Gold Coast, Australia, 9-11 April 2010

No change in insulin sensitivity following a single bout of resistance exercise in individuals with and without type 2 diabetes

B. A. Gordon[1], S. F. Fraser[2], S. R. Bird[1], A. C. Benson[1]
[1]School of Medical Sciences, RMIT University, Melbourne, Australia
[2]School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

Introduction

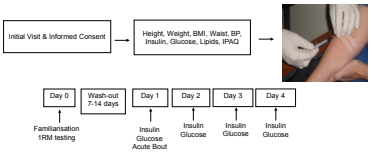
- Insulin sensitivity has been measured in response to a single acute bout of resistance exercise in previously healthy individuals [1-5] and people with type 2 diabetes [4, 6], but only for 36-hours in people without type 2 diabetes and 24 hours in those with type 2 diabetes.
- Post resistance exercise improvements to insulin sensitivity have been noted in individuals without type 2 diabetes [1, 7], while others have refuted this effect [2, 5, 8].
- The effect of resistance exercise appears to be more definitive in people with type 2 diabetes with both [4, 6] studies reporting improvements in insulin sensitivity.
- The aim of this study was to determine the length of time that improvements to insulin sensitivity and glucose transport remained following a single acute bout of resistance exercise; to determine the most effective frequency of resistance training.

Hypothesis

A single bout of moderate to high intensity resistance exercise will improve insulin sensitivity following this bout for 48 hours in people with type 2 diabetes compared with no change in people without type 2 diabetes.

Methodology

Study Design:
Ten sedentary (completing less than 20-minutes of aerobic exercise twice weekly), individuals without type 2 diabetes and 10 sedentary individuals with type 2 diabetes consented to participate after ethical approval. Baseline testing consisted of height, weight, lipid profile, fasting glucose and insulin, international physical activity questionnaire (IPAQ) and one-repetition maximum (1RM) strength testing on five exercises. After a 7-14 day washout period, participants underwent a single resistance exercise session before returning on each of the subsequent three days to undergo fasting blood testing.



Measurements:

Body Mass & Height: (c.v. = 0.3% & 0.10%)
Body Mass Index (BMI) – *(Weight (kg) / Height² (m))*

Waist Circumference (WC): (c.v. = 0.19%)

Bloods (fasting lipids, HbA1c, glucose, insulin: (c.v. = TC = 2%, HDL-C = 9%, LDL-C = 12%, TG = 3.5%, HbA1c = 3%, Glucose < 1%, Insulin = 13.6%)

1RM Testing:
A progressive protocol to failure on two consecutive attempts on the following exercises – bench press, 45° leg press, shoulder press, calf raises & lateral-pulldown.

Acute Resistance Exercise Bout:
The progressive exercise bout consisted of 3 sets of 10 repetitions for each exercise. Each set was completed at 45%, 60% and 75% of the participant's 1RM for each exercise with 60 seconds recovery between sets. Stretches were completed as a cool-down. This exercise bout took approximately 50 minutes to complete.

Statistical Analysis:
- Data are presented as mean (standard deviation), unless otherwise indicated.
- A two-way, mixed-between, repeated measures (group x time) analysis of variance (ANOVA) was completed to assess the change over time for insulin sensitivity, with independent t-tests comparing groups at individual time points.
- All data were analysed using SPSS version 17 for Windows with significance set at an alpha level of p<0.05.

Results

Participant demographics can be seen in Table 1 and shows that participants had normal lipid profiles and good glycaemic control, although two individuals without type 2 diabetes and five individuals with type 2 diabetes appeared to be hyperinsulinaemic (>130 pmol/l). Sixty percent of the participants without type 2 diabetes were overweight (40%) or obese (20%) with mean BMI = 25.8 (4.4) kg/m^2 while 90% of people with type 2 diabetes were overweight (50%) or obese (40%) with mean BMI = 29.6 (3.9) kg/m^2.

Table 1: Participant Demographics

Outcome	Type 2 Diabetes	No Diabetes
N	10	10
Male / Female	6/4	3 / 7
Age (years)	61.8 (7.2)	51.6 (5.8)*
Height (cm)	169.7 (7.7)	170.8 (7.9)
Weight (kg)	86.8 (13.4)	74.7 (10.0)*
Duration of Diabetes (years)	8.3 (5.1)	N/A
SBP (mmHg)	131 (20)	118 (13)
DBP (mmHg)	74 (8)	73 (9)
TC (mmol/l)	4.1 (0.6)	5.1 (0.8)*
LDL-C (mmol/l)	2.1 (0.4)	3.0 (0.4)*
HDL-C (mmol/l)	1.32 (0.22)	1.53 (0.47)
TG (mmol/l)	1.6 (0.6)	1.2 (0.9)
HbA1c (%)	6.8 (0.6)	5.6 (0.3)*
Fasting Glucose (mmol/l)	7.6 (1.6)	4.9 (0.5)*
Fasting Insulin (pmol/l)	137.9 (82.5)	95 (84.9)
MET-mins/wk (IPAQ)	423 (256)	987 (931)
Sitting Time (mins/wk, IPAQ)	468 (198)	378 (142)

* = significantly different between groups (p<0.05).

Results cont.

- There was a significant difference for fasting glucose levels between groups (p<0.01) at all time points.
- Mean insulin sensitivity was higher in the individuals without type 2 diabetes at all time points, but only statistically significant immediately prior to and following the resistance exercise bout (Figure 1).
- There were no within group differences found over time for either group in regards to fasting glucose, insulin or insulin sensitivity estimated using the Homeostasis Modelling Assessment (HOMA) equation.
- Individual variation in insulin sensitivity in response to a single resistance exercise bout is shown in figures 2 and 3 and indicates that while many of the participants had a similar response to the resistance exercise, some individuals responded differently, a point that warrants further investigation.

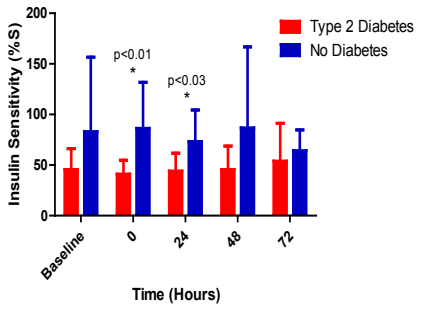


Figure 1: Mean insulin sensitivity (HOMA) before and after resistance exercise.

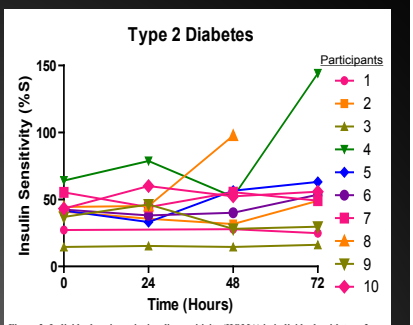


Figure 2: Individual variance in insulin sensitivity (HOMA) in individuals with type 2 diabetes.

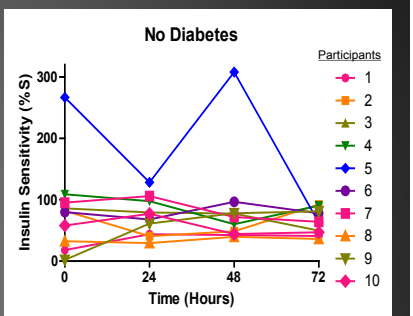


Figure 3: Individual variance in insulin sensitivity (HOMA) in individuals without type 2 diabetes.

Conclusion

- To our knowledge, this is the first study that has tracked the insulin response following a single resistance exercise bout for greater than 24-hours and 36–hours in people with and without type 2 diabetes respectively.
- There appears to be no change in insulin sensitivity following a single bout of resistance exercise in previously sedentary individuals with and without type 2 diabetes.
- This suggests further research is required to examine the effect of exercise intensity, type or the potential for change in each participant.

Where to Next?

- **Investigate the effect of an unfamiliar bout of resistance exercise on markers of inflammation and transient insulin resistance.**
- **Investigate whether participation in a regular resistance exercise program (chronic adaptation) changes this response.**

Acknowledgements

We would like to gratefully acknowledge the efforts and commitment of all of the participants involved in the study.

BAppSci (Human Movement), RMIT University, students for their valuable assistance with testing and training.

Brett Gordon is supported by a RMIT, School of Medical Sciences research scholarship.

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8. Howlett, KF., et al., Resistance exercise and insulin regulate AS160 and interaction with 14-3-3 in human skeletal muscle. Diabetes, 2007. 56(6): p. 1608-1614.

Abstract presented at RMIT University's Higher Degree by Research student conference 2010

Presentation Title: Consecutive oral glucose tolerance testing with or without prior resistance exercise does not affect insulin sensitivity in apparently healthy adults.
Name: Mr Brett Gordon
School: Medical Sciences

Introduction: Insulin sensitivity is a key component of type 2 diabetes (T2D) that decreases as the disease progresses. With the increasing prevalence of obesity and T2D, it is important to determine ways to improve insulin sensitivity and decrease the risk of future health conditions. Previous research has been unable to agree on the effects of a single session of resistance exercise and the length of time that these effects remain has not been fully investigated.

Statement of Problem/Aim: The benefits of exercise are well understood, however having people adhere to exercise guidelines is challenging. Therefore, the purpose of this study was to track the insulin sensitivity response to four-consecutive oral glucose tolerance tests (OGTT's) and assess the impact of a prior single resistance exercise bout to try to determine the optimum training frequency.

Outcomes: Twenty sedentary, apparently healthy individuals were recruited with ten (51.6±5.8 years) completing a single resistance exercise (RE) bout followed by four OGTTs on consecutive days and ten (54.6±6.5 years) completing four OGTTs on consecutive days without a prior resistance exercise bout (No-RE). At baseline, there was a significant difference in insulin sensitivity between groups according to the oral glucose insulin sensitivity index (RE=418.8±95.1ml.min^{-1}.m^{-2}; No-RE=333.6±71.9ml.min^{-1}.m^{-2}; p=0.04), however this difference was not present at any other time. There was no change in insulin sensitivity following repeated OGTT's, in either the RE or No-RE groups at any time point. It appears that repeated OGTT's provide a reliable estimate of insulin sensitivity in apparently healthy individuals however; a single moderate-high intensity resistance exercise bout did not produce a discernable change in insulin sensitivity between 24 and 96 hours after the exercise. The optimum training frequency is yet to be determined and therefore, the number of resistance exercise sessions required before changes to insulin sensitivity can be detected requires further investigation.

Gordon BA, Fraser SF, Bird SR, Benson AC. (2010) Consecutive oral glucose tolerance testing with or without prior resistance training does not affect insulin sensitivity in apparently healthy adults. Poster presentation at Higher Degree by Research Student Conference - Presenting Tomorrow's Knowledge, RMIT University, Melbourne, Australia, 20 October 2010.

Consecutive oral glucose tolerance testing with or without prior resistance training does not affect insulin sensitivity in apparently healthy individuals

B. A. Gordon[1], S. F. Fraser[2], S. R. Bird[1], A. C. Benson[1]
[1]School of Medical Sciences, RMIT University, Melbourne, Australia
[2]School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

Introduction

- Insulin sensitivity is a key component of type 2 diabetes that worsens as the disease progresses.
- The oral glucose tolerance test (OGTT) is used to diagnose type 2 diabetes and frequently to estimate insulin sensitivity; however, the effect of repeated, daily OGTT's is unclear.
- In apparently healthy individuals, insulin sensitivity has been reported to increase 24 hours following a single session of resistance exercise [1] and insulin action has been reported to increase approximately 36 hours following unaccustomed eccentric resistance exercise [2].
- Other studies however, have reported impaired insulin action following a single bout of resistance training [3].
- The primary aim of this study was to assess the impact of consecutive OGTT's on insulin sensitivity. The secondary aim was then to determine if a single, acute bout of resistance exercise resulted in improved insulin sensitivity and glucose transport and how long any changes remained; to determine the most effective frequency of resistance training.

Hypothesis

- Repeated, daily OGTT's will not affect insulin sensitivity.
- Insulin Sensitivity will improve for 48 hours following a single bout of moderate to high intensity resistance exercise.

Methodology

Study Design:
Twenty sedentary (completing less than 20-minutes of aerobic exercise twice weekly), apparently healthy individuals consented to participate after ethical approval. Baseline testing consisted of height, weight, lipid profile, fasting glucose and insulin, OGTT, international physical activity questionnaire (IPAQ) and one-repetition maximum (1RM) strength testing on five exercises in the group undertaking the resistance exercise bout. The study protocol is outlined in Figure 1.

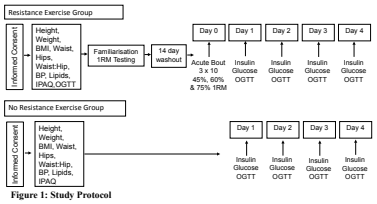

Figure 1: Study Protocol

Measurements:

Body Mass & Height: (c.v. = 0.3% & 0.10%)
Body Mass Index (BMI) – *(Weight (kg) / Height² (m))*

Waist Circumference (WC): (c.v. = 0.19%)

Bloods (fasting lipids, HbA1c, glucose, insulin: (c.v. = TC = 2%, HDL-C = 9%, LDL-C = 12%, TG = 3.5%, HbA1c = 3%, Glucose < 1%, Insulin = 8.45%)

1RM Testing:
A progressive protocol to failure on two consecutive attempts on the following exercises – bench press, 45° leg press, shoulder press, calf raises & lateral-pulldown.

Acute Resistance Exercise Bout:
The progressive exercise bout consisted of 3 sets of 10 repetitions for each exercise. Each set was completed at 45%, 60% and 75% of the participant's 1RM for each exercise with 60 seconds recovery between sets.

Oral Glucose Insulin Sensitivity (OGIS) and Area Under the Curve (AUC). OGIS and AUC are mathematical modeling equations that are validated against the euglycaemic hyperinsulinemic glucose clamp to predict insulin sensitivity from an OGTT.

Statistical Analysis:
- Data are presented as mean (standard deviation), unless otherwise indicated.
- A two-way, mixed-between, repeated measures (group x time) analysis of variance (ANOVA) was completed to assess the change over time for insulin sensitivity.
- All data were analysed using SPSS version 17 for Windows with significance set at an alpha level of p<0.05.

Results

Participant demographics can be seen in Table 1 and shows that participants had normal lipid profiles, blood pressure and good glycaemic control. The mean BMI for the resistance exercise group was 25.8 (4.5) kg/m² while it was 33.3 (6.3) kg/m² for the no resistance exercise group. One individual from the resistance exercise group and two from the no resistance exercise group had an abnormal response to the initial OGTT that would indicate they had impaired glucose tolerance. Two individuals from the resistance exercise group and four from the no resistance exercise group were hyperinsulinaemic (>130 pmol/L) at baseline.

Table 1: Participant Demographics

Measure	Resistance Exercise	No Resistance Exercise
Male / Female	3 / 7	3 / 7
Age (years)	51.6 (5.8)	54.6 (6.5)
Weight (kg)	74.7 (10.0)	93.4 (16.4)*
Height (cm)	170.8 (7.9)	167.7 (6.8)
BMI (kg.m^{-2})	25.8 (4.5)	33.3 (6.3)*
Waist:Hip	0.83 (0.07)	0.88 (0.08)
BP (mmHg)	120 (13) / 74 (9)	126 (14) / 83 (10)*
Cholesterol (mmol/L)	5.1 (0.8)	4.9 (1.2)
LDL (mmol/L)	3.0 (0.4)	2.8 (1.0)
HDL (mmol/L)	1.53 (0.47)	1.42 (0.24)
Triglycerides (mmol/L)	1.2 (0.9)	1.6 (0.5)
HbA1c (%)	5.6 (0.3)	5.5 (0.3)
Glucose (mmol/L)	4.9 (0.5)	5.4 (0.4)
Insulin (pmol/L)	95.6 (84.9)	129 (82.7)
MET-mins.wk^{-1} (IPAQ)	987 (931)	1428 (1365)
Sedentary Time (mins)	378 (142)	435 (207)

* = significantly different between groups (p<0.05). NB: only diastolic BP was different

Results cont.

- There was no change over time for area under the insulin curve for either group (Figure 2).
- The OGIS showed good reproducibility as there was no change over time for insulin sensitivity for either group (Figures 3 & 4).
- There was no change over time for 120 minute glucose levels for either group and no significant difference between groups (Figure 5).

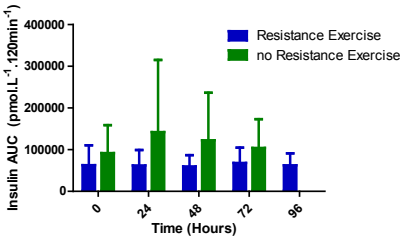

Figure 2: Mean (SD) area under the insulin curve for each OGTT.

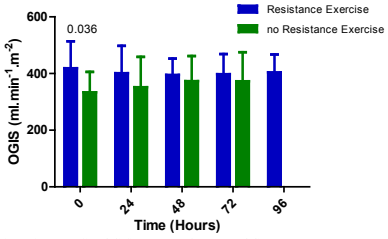

Figure 3: Mean (SD) OGIS calculated from each OGTT.

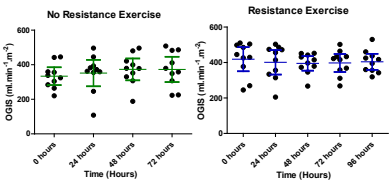

Figure 4: Variance in insulin sensitivity over time. Mean and 95% CI.

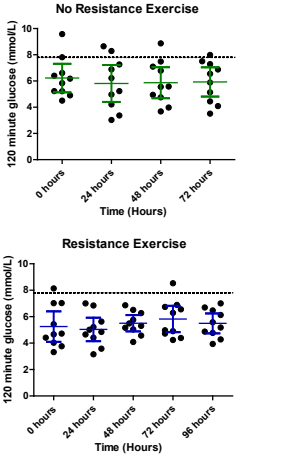

Figure 5: Variance in 120 minute glucose from the OGTT over time. Mean and 95% CI. Dotted line represents the cut off for a normal response.

Conclusion

- Repeated OGTT's provide a reliable estimate of insulin sensitivity in apparently healthy individuals that does not appear to be affected by administration on consecutive days.
- A single bout of moderate to high intensity resistance exercise did not produce a discernable change in insulin sensitivity.
- The OGTT produces moderately reproducible results in terms of glucose levels.

Where to Next?

- **Investigate the effect of an unfamiliar bout of resistance exercise on markers of inflammation and transient insulin resistance.**
- **Investigate the number of resistance exercise sessions required before changes to insulin sensitivity can be detected.**

Acknowledgements

We would like to gratefully acknowledge the efforts and commitment of all of the participants involved in the study.

BAppSci (Human Movement), RMIT University, students for their valuable assistance with testing and training.

Brett Gordon is supported by a RMIT, School of Medical Sciences research scholarship.

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1. Koopman, R., et al., A single session of resistance exercise enhances insulin sensitivity for at least 24 hours in healthy men. Euro J App Physiol, 2005. 94(1-2): p. 180-187.
2. King, D.S., et al., *Effects of eccentric exercise on insulin secretion and action in humans.* J Appl Physiol, 1993. 75(5): p. 2151-2156
3. Howlett, KF., et al., Resistance exercise and insulin regulate AS160 and interaction with 14-3-3 in human skeletal muscle. Diabetes, 2007. 56(6): p. 1608-1614.

Abstract presented at Australian Diabetes Society annual meeting in 2011

Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes

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Introduction

Long-term resistance exercise is known to improve glycaemic control.[1] However, the continuous glucose response to acute resistance exercise in untrained individuals with type 2 diabetes (T2D) treated with insulin are not known.

Methods

Seven individuals (males=4; females=3) with insulin treated T2D were recruited to participate, and their anthropometric, health and exercise capacity data recorded. Blood glucose levels were then monitored using the Medtronic iPro™2 continuous glucose monitoring system throughout the 24hrs prior to a single session of whole-body resistance exercise (3 sets, 10 repetitions at 70% one-repetition maximum) and for 3-days following the exercise session. Regular insulin and medication doses were maintained except for immediately before exercise where half the prescribed insulin dose was administered.

Results

Participants mean (SD) age was 56.0 (4.2) years, were diagnosed with T2D 15.3 (7.1) years ago, weighed 97.8 (40.1) kg with HbA1c of 8.2% (0.6)%. During the 24hrs pre-exercise intervention, participants experienced blood glucose $\geq$10mmol.L^{-1} (hyperglycaemia) for 15.9% of the day. Post-intervention, time in hyperglycaemia increased from pre-exercise by 22.0% (95%CI=-2.5 to 46.5), 20.6% (95%CI=4.1 to 37.1) and 24.3% (95%CI=1.8 to 46.8) between 0-24, 24-48 and 48-72 hours respectively. Whilst none of these differences reached statistical significance (probably due to the small sample size), a large effect size was noted (partial eta^2=0.737).

Conclusion

In novice exercisers, a single session of resistance exercise appears to impair glycaemic control, when measured continuously, for up to 72 hours post-exercise. These findings differ from those reported after a single session of aerobic exercise,[2] low-intensity resistance exercise combined with short high-intensity aerobic exercise,[3] or resistance exercise[4] (measured by oral glucose tolerance testing) and may be due to a suggested transient insulin resistance.[5] Our results suggest that resistance exercise may induce responses via a different

metabolic mechanism than aerobic or combined exercise. These mechanisms require further investigation.

References

(1) Dunstan DW., et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. Diabetes Care. 2002;25(10):1729-1736
(2) Manders, RJF., et al. Low-intensity exercise reduces the prevalence of hyperglycemia in type 2 diabetes. Med Sci Sports Exerc. 2010;42(2):219-225
(3) Praet, SF., et al. Influence of acute exercise on hyperglycemia in insulin-treated type 2 diabetes. Med Sci Sports Exerc. 2006;38(12):2037-2044
(4) Fluckey JD., et al. Effects of resistance exercise on glucose tolerance in normal and glucose-intolerant subjects. J Appl Physiol 1994;77(3):1087-1092
(5) Kirwan. JP. & del Aguila LF. Insulin signalling, exercise and cellular integrity. Biochem Soc Trans. 2003;31(Pt 6):1281-1285

Gordon BA, Bird SR, MacIsaac RJ, Benson AC. (2011). Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes. Poster presentation at 2011 ADS/ADEA Annual Scientific Meeting, Perth, Australia, 31 August – 2 September 2011.

Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes

B. A. Gordon[1,2], S. R. Bird[1], R. J. MacIsaac[3], A. C. Benson[1]

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[3]Endocrine Centre, Austin Health & University of Melbourne, Melbourne, VIC, Australia

Introduction

Current treatment recommendations for type 2 diabetes suggest that metformin and lifestyle interventions be implemented immediately and that early implementation of insulin therapy is employed to achieve and maintain glycaemic control [1]. It has been reported that individuals with type 2 diabetes experience hyperglycaemia (blood glucose >10 mmol/L) for up to 40% of a single day [2].

Long-term resistance exercise is known to improve glycaemic control in people with type 2 diabetes being treated with diet or oral medications [3]. However, this has only been determined using a one-off 'snapshot' method such as a blood test or oral glucose tolerance test. Continuous glucose monitoring (CGM) has shown the prevalence of hyperglycaemia can be reduced with single session of aerobic exercise [4] or aerobic exercise combined with resistance exercise [5]. The amount of time spent in hyperglycaemia is an important aspect of diabetes control that can only be determined through CGM.

Therefore, the purpose of this study was to investigate the effect of a single session of resistance exercise, on glucose homeostasis using CGM.

Methodology

Study Design:
Eleven individuals with insulin treated type 2 diabetes consented to participate after ethical approval. The study protocol is outlined in Figure 1. Participants consumed a standardised dinner meal on the evening before each scheduled visit, while a standardised breakfast meal was consumed at each visit. Regular insulin and medication doses were maintained except for immediately before exercise, where half the prescribed insulin dose was administered.

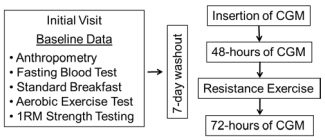

Figure 1: Study Protocol

Baseline Testing:

Body Mass & Height: (c.v. = 0.3% & 0.10%)
Body Mass Index (BMI) = *(Weight (kg) / Height² (m))*

Bloods (fasting lipids, HbA1c, glucose, insulin, hs-CRP: (c.v.= TC=2.0%, HDL-C=9.0%, LDL-C=12.0%, TG=3.5%, HbA1c=3.0%, Glucose=4.5%, Insulin=8.5%, hsCRP=6.0%)

Physical Activity:
Activity volume and sedentary time were evaluated using the short-form International Physical Activity Questionnaire [6].

VO_{2peak} Testing:
An incremental cycle protocol was performed on a Lode (Excalibur Sport) cycle ergometer with initial workload (Watts) related to participants body weight and increased by 25% of the initial workload every 150 seconds.

1RM Testing:
A progressive protocol to failure on two consecutive attempts for bench press, 45° leg press, lateral pulldown, knee extension, seated row & knee flexion.

Resistance Exercise Intervention:

Acute Resistance Exercise Bout:
The resistance exercise bout consisted of 3 sets of 10 repetitions of each exercise. The load for each set was 70% of the participant's 1RM with a recovery period of 60-90 seconds between sets.

Continuous Glucose Monitoring:
A Medtronics iPro™2 CGM was inserted two days prior to and was removed three days after completing the resistance exercise bout. Data was downloaded to a computer for calculation of hyperglycaemia and area under the curve (AUC).

Statistical Analysis:
- Data are presented as mean (standard deviation), unless otherwise indicated.
- A repeated measures analysis of variance (ANOVA) was completed to assess the change over time for area under the 24 hour glucose curve and percentage of time spent in hyperglycaemia (blood glucose >10 mmol/L).
- All data were analysed using SPSS version 18 for Windows with significance set at an alpha level of p=0.05.

Results

Participant demographics can be seen in Table 1 and shows that participants had good lipid profiles, blood pressure and poor glycaemic control. According to BMI, on average participants were classified as obese. On average, participants completed a moderate volume of physical activity and spent a large amount of time being sedentary [6]. Participants also had a poor level of aerobic fitness and muscular strength. In the 24 hours prior to completing the resistance exercise, participants experienced hyperglycaemia on average for 25% of the day. Whilst this did not change significantly following exercise (p=0.53; Figure 2), a large effect size was found (partial eta^2=0.23). There was also no statistically significant change to area under the 24-hour glucose curve (p=0.23) at any time following the resistance exercise bout, although again a large effect size was found (partial eta^2=0.40; Figure 3).

Table 1: Participant Demographics

Measure	Mean (SD)
Male / Female	6 / 5
Age (years)	58.9 (7.2)
Years of Diabetes	16.3 (8.5)
Weight (kg)	95.5 (37.0)
Height (cm)	167.1 (11.5)
BMI ($kg.m^{-2}$)	33.6 (10.0)
BP (mmHg)	133(17) / 80 (9)
Cholesterol (mmol/L)	4.2 (0.7)
LDL (mmol/L)	2.3 (0.5)
HDL (mmol/L)	1.18 (0.37)
Triglycerides (mmol/L)	1.6 (0.8)
HbA1c (%)	8.0 (0.6)
Glucose (mmol/L)	8.1 (2.0)
Insulin (mIU/L)	33.1 (75.8)
hsCRP (mg/L)	4.7 (7.3)
Activity ($MET\text{-}mins.wk^{-1}$)	1068 (2047)
Sedentary Time (mins)	455 (315)
VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	19.8 (6.9)
Bench Press 1RM (kg)	39.6 (17.2)

BMI = body mass index; BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoproetin; HbA1c = glycated haemoglobin; hsCRP = high sensitivity C-reactive protein; VO_{2peak} = peak oxygen uptake; 1RM = one repetition maximum

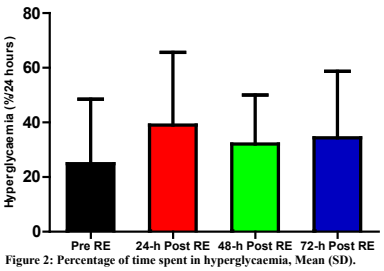

Figure 2: Percentage of time spent in hyperglycaemia, Mean (SD).
RE = resistance exercise; 24-h = 24 hours; 48-h = 48 hours; 72-h = 72 hours

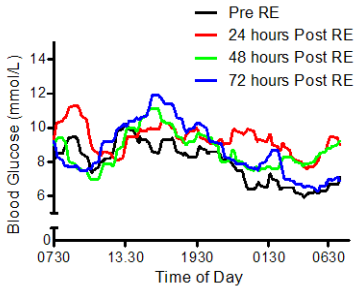

Figure 3: 24 hour glucose levels prior to and following resistance exercise.
RE = Resistance Exercise

Conclusion

- In novice exercisers, a single session of resistance exercise may impair glycaemic control when measured continuously for up to 72 hours after resistance exercise.

  This finding is in contrast to those reported after a single session of aerobic exercise [4] or low-intensity resistance exercise combined with short high-intensity aerobic exercise [5]. It also differs to that reported following resistance exercise of a similar intensity when insulin sensitivity was estimated using oral glucose tolerance testing (OGTT) [7]. This may be due to the suggested transient insulin resistance [8] or it may be that our results using CGM provide a more complete picture of the response compared to a 'snapshot' view obtained from fasting blood samples or OGTT. Our results however, suggest that resistance exercise induces responses via different metabolic mechanisms to aerobic and combined exercise.

- It is not known whether this level of variation is similar or different to daily biological variation in 24-hour glucose levels.

Where to Next?

- **Investigate the daily variation of 24-hour glucose levels under free living conditions without modifying medication or activity levels.**
- **Investigate whether the response to a single session of resistance exercise is similar in people who have regularly completed resistance training for at least six months.**
- **Compare the mechanisms responsible for adaptation to resistance and aerobic exercise.**

Acknowledgements

This study was completed thanks to funding received from the Australian Technology Network's Centre for Metabolic Fitness.

We would like to gratefully acknowledge the efforts and commitment of all of the participants involved in the study.

BAppSci (Human Movement), RMIT University, students for their valuable assistance with testing and training.

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Abstract presented at RMIT University's Higher Degree by Research student conference 2011

Presentation Title: **Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes**

Name: Mr Brett Gordon
School: Medical Sciences

Introduction: Long-term resistance exercise is known to improve glycaemic control however, less is known about the effects from a single session of resistance exercise. Reducing postprandial hyperglycaemic excursions is considered integral in treating type 2 diabetes (T2D) with recent data suggesting individuals with T2D experienced hyperglycaemia for almost 40% of a single day.

Statement of Problem/Aim: As prescription of exogenous insulin therapy is increasing in T2D, we sought to investigate the response to resistance exercise in untrained individuals with T2D treated with insulin using continuous glucose monitoring.

Outcomes: Eleven individuals (males=6; females=5) with insulin treated T2D and a mean (SD) age of 58.9 (7.2) years consented to participate. Participants were diagnosed with T2D 16.3 (8.5) years ago, weighed 95.5 (37.0) kg with HbA1c of 8.0% (0.6)%. Blood glucose levels were monitored using the Medtronic iPro™2 continuous glucose monitoring system throughout the 24hrs prior to a single session of whole-body resistance exercise (3 sets, 10 repetitions at 70% one-repetition maximum) and for 3-days following the exercise session. Regular insulin and medication doses were maintained except for when the insulin dose was halved immediately before exercise. During the 24hrs pre-exercise intervention, participants experienced blood glucose $\geq$10mmol.L^{-1} (hyperglycaemia) for 24.9% of the day. Post-exercise, time in hyperglycaemia increased from pre-exercise by 14.1% (95%CI:-14.6 to 42.8), 7.2% (95%CI:-20.6 to 35.0) and 9.5% (95%CI:-26.2 to 45.1) between 0-24, 24-48 and 48-72 hours respectively. Whilst none of these differences reached statistical significance (probably due to the small sample size), a large effect size was noted (partial eta^2=0.228). These findings differ from those reported after a single session of aerobic exercise or low-intensity resistance exercise combined with short high-intensity aerobic exercise and suggests that in novice exercisers, a single session of resistance exercise appears to impair glycaemic control, when measured continuously, for up to 72 hours post-exercise.

Gordon BA, Bird SR, MacIsaac RJ, Benson AC. (2011). Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes. Poster presentation at Higher Degree by Research Student Conference – Vision to Reality, RMIT University, Melbourne, Australia, 21 October 2011.

Continuous glucose response to a single session of resistance exercise in individuals with insulin requiring type 2 diabetes

B. A. Gordon[1,2], S. R. Bird[1], R. J. MacIsaac[3], A. C. Benson[1]

[1]School of Medical Sciences & Health Innovations Research Institute, RMIT University, Melbourne, Australia
[2]Physiotherapy Department, Austin Health, Melbourne, Australia
[3]Endocrine Centre, Austin Health & University of Melbourne, Melbourne, VIC, Australia

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Study Design:
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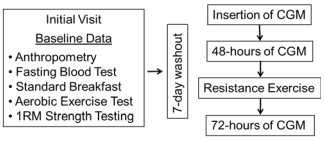

Figure 1: Study Protocol

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Acute Resistance Exercise Bout:
The resistance exercise bout consisted of 3 sets of 10 repetitions of each exercise. The load for each set was 70% of the participant's 1RM with a recovery period of 60-90 seconds between sets.

Continuous Glucose Monitoring:
A Medtronics iPro™2 CGM was inserted two days prior to and was removed three days after completing the resistance exercise bout. Data was downloaded to a computer for calculation of hyperglycaemia and area under the curve (AUC).

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- Data are presented as mean (standard deviation), unless otherwise indicated.
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Results

Participant demographics can be seen in Table 1 and shows that participants had good lipid profiles, blood pressure and poor glycaemic control. According to BMI, on average participants were classified as obese. On average, participants completed a moderate volume of physical activity and spent a large amount of time being sedentary [6]. Participants also had a poor level of aerobic fitness and muscular strength. In the 24 hours prior to completing the resistance exercise, participants experienced hyperglycaemia on average for 25% of the day. Whilst this did not change significantly following exercise (p=0.53; Figure 2), a large effect size was found (partial eta²=0.23). There was also no statistically significant change to area under the 24-hour glucose curve (p=0.23) at any time following the resistance exercise bout, although again a large effect size was found (partial eta²=0.40; Figure 3).

Table 1: Participant Demographics

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Male / Female	6 / 5
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Weight (kg)	95.5 (37.0)
Height (cm)	167.1 (11.5)
BMI (kg.m^{-2})	33.6 (10.0)
BP (mmHg)	133(17) / 80 (9)
Cholesterol (mmol/L)	4.2 (0.7)
LDL (mmol/L)	2.3 (0.5)
HDL (mmol/L)	1.18 (0.37)
Triglycerides (mmol/L)	1.6 (0.8)
HbA1c (%)	8.0 (0.6)
Glucose (mmol/L)	8.1 (2.0)
Insulin (mIU/L)	33.1 (75.8)
hsCRP (mg/L)	4.7 (7.3)
Activity (MET-mins.wk^{-1})	1068 (2047)
Sedentary Time (mins)	455 (315)
VO_{2peak} (ml.kg^{-1}.min^{-1})	19.8 (6.9)
Bench Press 1RM (kg)	39.6 (17.2)

BMI = body mass index; BP = blood pressure; LDL = low-density lipoprotein; HDL = high-density lipoproetin; HbA1c = glycated haemoglobin; hsCRP = high sensitivity C-reactive protein; VO_{2peak} = peak oxygen uptake; 1RM = one repetition maximum

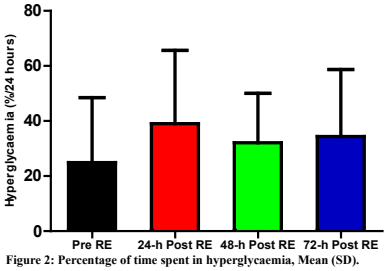

Figure 2: Percentage of time spent in hyperglycaemia, Mean (SD).
RE = resistance exercise; 24-h = 24 hours; 48-h = 48 hours; 72-h = 72 hours

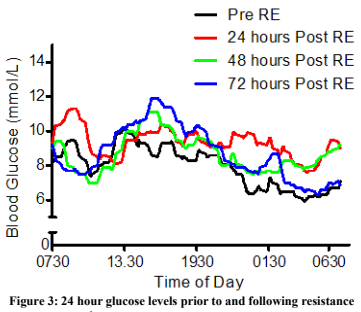

Figure 3: 24 hour glucose levels prior to and following resistance exercise.
RE = Resistance Exercise

Conclusion

- In novice exercisers, a single session of resistance exercise may impair glycaemic control when measured continuously for up to 72 hours after resistance exercise.

  This finding is in contrast to those reported after a single session of aerobic exercise [4] or low-intensity resistance exercise combined with short high-intensity aerobic exercise [5]. It also differs to that reported following resistance exercise of a similar intensity when insulin sensitivity was estimated using oral glucose tolerance testing (OGTT) [7]. This may be due to the suggested transient insulin resistance [8] or it may be that our results using CGM provide a more complete picture of the response compared to a 'snapshot' view obtained from fasting blood samples or OGTT. Our results however, suggest that resistance exercise induces responses via different metabolic mechanisms to aerobic and combined exercise.

- It is not known whether this level of variation is similar or different to daily biological variation in 24-hour glucose levels.

Where to Next?

- **Investigate the daily variation of 24-hour glucose levels under free living conditions without modifying medication or activity levels.**
- **Investigate whether the response to a single session of resistance exercise is similar in people who have regularly completed resistance training for at least six months.**
- **Compare the mechanisms responsible for adaptation to resistance and aerobic exercise.**

Acknowledgements

This study was completed thanks to funding received from the Australian Technology Network's Centre for Metabolic Fitness.

We would like to gratefully acknowledge the efforts and commitment of all of the participants involved in the study.

BAppSci (Human Movement), RMIT University, students for their valuable assistance with testing and training.

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